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TOBACCO SMOKING AS A POSSIBLE ETIOLOGIC FACTOR IN BRONCHIOGENIC CARCINOMA

A Study of Six Hundred and Eighty-Four Proved Cases

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General Increase.—There is rather general agreement that the incidence of bronchiogenic carcinoma has greatly increased in the last half-century. Statistical studies at the Charity Hospital of New Orleans (Ochsner and DeBakey),[1] the St. Louis City Hospital (Wheeler)[2] and the Veterans Administration Hospital of Hines, Ill. (Avery)[3] have revealed that at these hospitals cancer of the lung is now the most frequent visceral cancer in men.

Autopsy statistics throughout the world show a great increase in the incidence of bronchiogenic carcinoma in relation to cancer in general. Kenneway and Kenneway,[4] in a careful statistical study of death certificates in England and Wales from 1928 to 1945, have presented undoubted evidence of a great increase in deaths from cancer of the lung. In this country statistics compiled by the American Cancer Society show a similar trend during the past two decades.[5]

Tobacco as a Possible Cause of Increase.—The suggestion that smoking, and in particular cigaret smoking, may be important in the production of bronchiogenic carcinoma has been made by many writers on the subject even though well controlled and large scale clinical studies are lacking. Adler[6] in 1912 was one of the first to think that tobacco might play some role in this regard. Tylecote,[7] Hoffman,[8] McNally,[9] Lickint,[10] Arkin and Wagner,[11] Roffo[12] and Maier[13] were just a few of the workers who thought that there was some evidence that tobacco was an important factor in the increase of cancer of the lungs. Müller[14] in 1939, from a careful but limited clinical statistical study, offered good evidence that heavy smoking is an important etiologic factor. In 1941 Ochsner and DeBakey[15] called attention to the similarity of the curve of increased sales of cigarets in this country to the greater prevalence of primary cancer of the lung. They emphasized the possible etiologic relationship of cigaret smoking to this condition. In a recent paper Schrek[16] concluded that there is strong circumstantial evidence that cigaret smoking is an etiologic factor in cancer of the respiratory tract and finds that his data are in agreement with the results of a preliminary report presented by Wynder and Graham at the National Cancer Conference in February 1949.[17]

Purpose of Study.—The purpose of the present study was to attempt to determine, so far as possible by clinical investigations, statistical methods and experimental studies, the importance of various exogenous factors that might play a role in the induction of bronchiogenic carcinoma. In this regard we intended to learn the relative importance of previous diseases of the lungs, rural and urban distribution of patients, various occupations and hereditary background as well as smoking habits. By obtaining all this information, we hoped to determine whether any of these factors, either singly or in combination, have had an effect in increasing the incidence of bronchiogenic carcinoma.

In the present paper the chief emphasis will be placed on our findings in regard to smoking.

METHOD OF STUDY

The results of this study are based on 684 cases of proved bronchiogenic carcinoma. It should be emphasized that the results in this report have not been obtained from hospital records since we learned at the outset of our study that the routine records did not supply satisfactory answers to our questions. It was therefore decided to seek the desired information by special interviews. Six hundred and thirty-four patients reported on in this paper have been personally interviewed, and in 33 cases we obtained the information by mailing a questionnaire.[18] In the remaining 17 cases information for the questionnaire was obtained from a person who had been intimately acquainted with the patient throughout his adult life.

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This study has been aided by a grant from the American Cancer Society. Other phases of it will be presented in subsequent publications.

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17. Wynder, E. L., and Graham, E. A.: Tobacco and Bronchiogenic Carcinoma: Preliminary report to the National Cancer Conference, Memphis, February 1949.
18. The questionnaires were sent to male and female patients with cancer of the lungs from Dr. W. L. Watson's Thoracic Surgery Service at Memorial Hospital, New York.

Through the cooperation of many hospitals and physicians throughout all parts of the country who permitted us to interview their patients, it is felt that a fairly good cross section of the entire United States has been obtained. The list of cooperating institutions and physicians is presented below.[19]

In order to make this survey as uniform as possible, each interviewer used the questionnaire shown in table 1.

In regard to smoking habits, we considered it particularly essential to learn how much a patient had smoked formerly, even though he might not smoke at all or smoke little at the time of the interview. The reason for this is the well known existence of a time lag between the exposure to a carcinogenic substance and the appearance of cancer. Many patients coming into the hospital with chronic disease of the lungs had stopped smoking months, or even years, previously. We therefore asked the patients to estimate the average use of tobacco during the last twenty years of their smoking period. The control patients were questioned in an identical manner; thus any possible error lying in this method of estimating smoking habits was balanced.

In questioning patients about occupations, we attempted to learn all the occupations of a given patient, the years during which he had held these jobs and to what type of dusts or fumes he had been exposed. Similar details were obtained in regard to other possible exposures, such as those a patient might have had in connection with certain hobbies.

Classification of Smoking.—In order to facilitate a statistical analysis of the results, the arbitrary classification of smoking habits given in table 2 was established. If a patient smoked for less than twenty years, his amount of smoking was adjusted to a twenty year period. Thus a patient smoking 20 cigarets for ten years only was classified as smoking 10 cigarets daily (class 2). Such adjustments were rarely necessary, since only a few patients had smoked for less than twenty years.

If a man smoked habitually more than one type of tobacco during the last twenty years, the various types were added together to make up his classification. Thus a man who smoked 1 package of cigarets daily, as well as 2 cigars, was classified as a class IV, or an excessive, smoker.

Histologic Types:—To insure an undoubted diagnosis, microscopic confirmation of the presence of carcinoma was obtained in all cases. Some difficulty arose in the histologic classification because of the variation of terms employed by pathologists in the different hospitals who examined the specimens. For example, what some pathologists would designate as an adenocarcinoma others would classify as an undifferentiated carcinoma. Likewise, the term oat cell or round cell carcinoma was at times used, a designation which is not recognized by some pathologists. In some cases pathologists called a lesion, from biopsy section, merely a carcinoma, unclassified. It may be said, however, that in general by far the most prevalent histologic types were the epidermoid or squamous carcinoma and its variant the undifferentiated carcinoma. These are the most common types found in males. In females the adenocarcinoma has so far been nearly as common as the other types. It is unquestionably the epidermoid and undifferentiated carcinomas which have shown the

TABLE 1.—*Etiologic Survey*

Name:..... Age:.....

1. Have you ever had a lung disease? If so, state time, duration and site of disease:
   Pneumonia Asthma Tuberculosis Bronchiectasis
   Influenza Lung Abscess Chest Injuries Others
2. Do you or did you ever smoke? Yes ☐ No ☐
3. At what age did you begin to smoke?
4. At what age did you stop smoking?
5. How much tobacco did you average per day during the past 20 years of your smoking?
   Cigarettes.....Cigars.....Pipes.....
6. Do you inhale the smoke? Yes ☐ No ☐
7. Do you have a chronic cough which you attribute to your smoking, especially upon first smoking in the morning? If so, for how long? Yes ☐ No ☐
   Duration.....
8. Do you smoke before or after breakfast? Before ☐ After ☐
9. Name the brand or brands, and dates, if any given brand has been smoked exclusively for more than five years.
   Change frequently? ☐

First brand—from 19.... to 19....

Second brand—from 19.... to 19....

10. What kind of jobs have you held? Have you been exposed to dust or fumes while working there? (Use back of page for detailed description of possible exposure)

From	To	Position	Dust or Fumes

11. Have you ever been exposed to irritative dusts or fumes outside of your job? In particular have you ever used insecticide spray excessively? If so, state time and duration.
    Yes ☐ No ☐ Type..... Duration.....
12. How much alcohol do you or have you averaged per day? State time and duration in years.
    Whiskey..... Beer..... Wine.....
13. Where were you born and where have you lived most of your life? State the approximate time span you have lived in a certain locality. Up to what grade did you attend school?
    Birthplace.....Home.....Educational Level.....
14. State the cause of death of your parents, and of brothers and sisters if any.
15. *Site of Lesion* *Microscopic Diagnosis* *Papanicolaou Class* *Etiological Class*

Interviewer .....

19. CALIFORNIA: Private patients of Drs. L. Brewer, Daniels, F. Dolley, D. Dugan, H. Garland, E. Holman, J. Jones, W. Rogers, P. Samson, B. Stephens. Hospitals: Birmingham General, French, Good Samaritan, Letterman General, Los Angeles County, Southern Pacific General, Stanford, United States Marine, United States Naval, University of California, Wadsworth General. COLORADO: Private patients of Drs. A. Brown, F. Condon, J. Grow, F. Harper, M. Peck. Hospitals: Colorado General, Denver General, Fitzsimmons, Fort Logan Veterans, General Rose, St. Lukes. DISTRICT OF COLUMBIA: Private patients of Drs. B. Blades, E. Davis. Hospitals: Georgetown, George Washington, Walter Reed. ILLINOIS: Hospitals: Cook County, Veterans Administration, Hines, Ill. MARYLAND: Hospitals: Johns Hopkins, United States Naval. MASSACHUSETTS: Private patients of Drs. D. Harken, R. Overholt. Hospitals: Boston City, Massachusetts General, New England Deaconess. MICHIGAN: Hospitals: Dearborn Veterans. MISSOURI: Private patients of Drs. J. Flance, A. Goldman, R. Smith. Hospitals: Jefferson Barracks Veterans, Jewish, St. Louis City, St. Louis County. NEW JERSEY: Hospitals: Berthold S. Pollack, Newark City. NEW YORK: Private patients of Drs. W. Cahan, H. Maier, J. Pool, W. Watson. Hospitals: Bellevue, Veterans Administration, Brooklyn Cancer Institute, Kings County Memorial, Montefiore, New York City Cancer Institute, New York Hospital, Presbyterian, Roswell Park Memorial Institute. OHIO: Hospitals: Veterans Administration. PENNSYLVANIA: Private patients of Dr. J. Johnson. Hospitals: Jefferson Medical College, Temple University, University of Pennsylvania. UTAH: Private patients of Drs. W. Rumel, Cutler. Hospitals: Holy Cross, St. Marks, Salt Lake County General, Veterans Administration, Dr. W. H. Groves, Latter-Day Saints.

greatest increase in recent years. For this reason we were particularly interested in studying these types separately from the adenocarcinomas. The present report includes 605 male and 25 female patients with epidermoid, undifferentiated and unclassified carcinomas and 39 male and 15 female patients with adenocarcinoma. In order to determine possible sex variations in the etiology of cancer of the lung, results in men and women are reported separately.

Control Study I.—To check all possible bias on the part of the interviewers who saw only patients believed to have bronchiogenic carcinoma, it was deemed advisable to conduct a control study in which a nonmedical investigator would interview every patient admitted to the Chest Service of Barnes Hospital without knowing the diagnosis in advance. Two interviewers [20] were used for this purpose. When the final diagnosis was determined, all cases of cancer of the lungs (75 men) were separated from the other cases (132). Control patients under the age of 30 were excluded since there were no cases of cancer in this age group. Seventeen male patients for whom no definitive diagnosis could be made were also omitted.

In addition these interviewers interrogated patients with cancer of the lung at other St. Louis hospitals,[21] also without previous knowledge of diagnosis. Here the interviewers were given the names of several patients with diseases of the chest in a comparable age group, of whom at least 1 was suspected to have bronchiogenic carcinoma. The patients with proved cancer of the lung (25 men) and the other patients (54 men) were added to the Barnes Hospital groups, thus collectively making up control study I.

To determine the smoking habits, as well as the other data contained in the questionnaire of our study of other hospital patients, the nonmedical investigators also questioned patients without cancer of the lungs on the general surgical and medical services at Barnes Hospital, the Jefferson Barracks Veterans Hospital and the St. Louis City Hospital. This group, called "general hospital population," consists of 780 patients. Also a total of 552 female patients without cancer of the lungs have been interviewed as control patients on our surgical and medical services.

Two objects were to be realized by this control study. One was to learn of possible exposures to exogenous irritants of a large group of patients without cancer of the lung and the other to test the validity of the interviews made by those who knew the suspected diagnosis in a given case in advance.

Age Distribution in Control Cases: For proper statistical evaluation of a study of this kind it is obvious that the age distribution should be the same in the control cases as in the cases of cancer of the lungs. Since no patients with cancer of the lungs below 30 or above 80 years of age were seen, no controls beyond these ages have been included. The controls comprised the unselected patients as they entered the Barnes Hospital and other St. Louis hospitals. For that reason their age distribution is not identical with that of the patients with cancer. In order to be able to evaluate the cases without cancer on the basis of the same age distribution as that found in the cases of cancer, the following adjustments were made:

The combined results include data on 780 cases without cancer. Among these there is the following age distribution: 30 to 39, 18.7 per cent; 40 to 49, 21 per cent; 50 to 59, 26.9 per cent; 60 to 69, 20.5 per cent, and 70 to 79, 12.8 per cent. (For the age distribution in the 605 cases of cancer see table 5.)

The smoking classifications of the control cases have been made proportional to the age distribution among the cases of cancer by multiplying the percentage value of each smoking classification for each age group of the controls by the proportion of cases of cancer in that age group. For example, in the age group 30 to 39 of the controls there were 146 (18.7 per cent) patients, of whom 20 (13.6 per cent) were nonsmokers. However, since of the patients with cancer only 2.3 per cent fell into this age group, the value of 13.6 per cent was made proportional to the age distribution in the cases of cancer (2.3 per cent).[22] In a similar manner the smoking values for the control group aged 40 to 49 were made proportional to 17.4 per cent. Finally, the quotients of the smoking classifications in each age group were added to make the percentage values shown in figure 3. The detailed data which compare the smoking classifications of the two groups according to age are shown in table 6. It was from those data that the proportional values were obtained.

TABLE 2.—*Classification of Smoking Habits*

Group 0.....	Nonsmokers (Less than 1 cigaret per day for more than 20 years) *
1.....	Light smokers (From 1 to 9 cigarets per day for more than 20 years) * †
2.....	Moderately heavy smokers (From 10 to 15 cigarets per day for more than 20 years) *
3.....	Heavy smokers (From 16 to 20 cigarets per day for more than 20 years) *
4.....	Excessive smokers (From 21 to 34 cigarets per day for more than 20 years) *
5.....	Chain smokers (35 cigarets or more per day for at least 20 years) *

* Pipe and cigar smokers have been included by arbitrarily counting 1 cigar as 5 cigarets and 1 pipeful as 2½ cigarets.
† Includes minimal smokers (from 1 to 4 cigarets a day, or the equivalent in pipes or cigars for more than 20 years).

The 100 cases of cancer and the 186 cases of control study I were made proportional in the same manner.

Control Study II.—In addition to the control study just cited, it was thought to be valuable to have other physicians carry out similar interviews using our questionnaire. It was thought that the results would serve as an effective control for the cases collected under our own supervision.

At this time we are reporting preliminary results based on 83 patients interviewed at the Bellevue Hospital, Columbia University Division (New York), by Dr. H. G. Turner [23]; at the Boston City Hospital by Dr. G. W. Ware [24]; at the Crile Veterans Hospital (Cleveland, Ohio) by Dr. C. T. Surington, and at the Veterans Administration Hospital, Hines, Ill., by Dr. E. J. Shabart.

RESULTS

The first data to be presented are based on 605 proved cases of bronchiogenic carcinoma in men, other than adenocarcinoma. Five hundred and ninety-five of these cases have been diagnosed on the basis of tissue biopsy,

20. Betty G. Proctor, A.B., and Adele B. Croninger, M.A.
21. City Hospital, Jewish Hospital and Veterans Administration Hospital.

22. $\frac{13.6 \times 2.3}{100} = 0.312$. This is the quotient which, added to the others determined in the same manner, makes the data shown in figure 3.
23. Of the service of Dr. James B. Amberson.
24. Of the service of Dr. John W. Strieder.

9 on the basis of examination of sputum and 1 on the basis of study of the pleural fluid.[25]

Comparison of Independent Studies.—Before the smoking habits of the 605 patients with cancer of the lungs are compared with those of the general hospital population, it might be well to compare the results in the two control studies and the group of 422 patients (study III) interviewed and collected by one of us

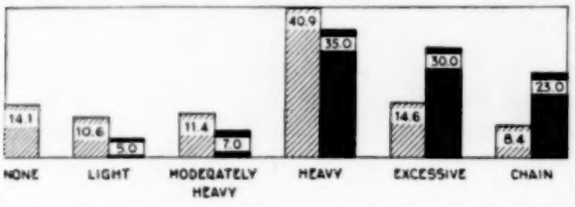

Fig. 1.—Control study I. Amount of smoking in percentage among 100 male patients with cancer of the lungs (solid bars) and 186 male patients with other chest diseases (lined bars) having the same age and economic distribution.

(E. L. W.) to determine any possible bias in cases in which the suspected diagnosis was known in advance and whether the data are sufficiently similar to warrant their discussion as a group.

Control Study I: This group consists of 100 patients with cancer of the lungs and 186 with diseases of the chest other than cancer interviewed by two nonmedical investigators who had no previous knowledge of the diagnosis in a given case. The data show no nonsmokers (fig. 1) among the cancer group, while there are 14.1 per cent nonsmokers among the patients with other thoracic diseases. Ninety-five per cent of the patients with cancer are in the classification of moderately heavy to chain smokers and 53 per cent are excessive and chain smokers, while among the patients without cancer, 75.3 and 23 per cent, respectively, fell among these smoking groups.

Control Study II: The data in table 3 cover 83 male patients with cancer of the lungs interviewed independently by physicians in other cities. Among each small group of cases some variation is, of course, to be expected. In each of the individual groups nearly half or more of the patients are excessive or chain smokers. Grouping the data of the four independent investigators together, we find 2.4 per cent nonsmokers and 93.9 per cent moderately heavy to chain smokers (fig. 2), while

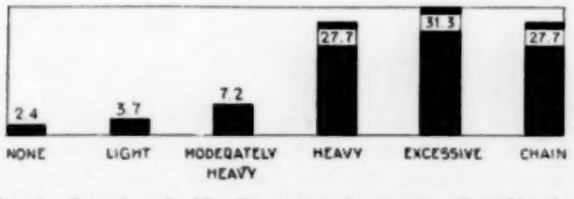

Fig. 2.—Control study II. Percentages for amount of smoking in 83 cases of cancer of the lungs collected independently by Dr. E. J. Shabart (Chicago), Dr. C. T. Surington (Cleveland), Dr. H. G. Turner (New York) and Dr. G. W. Ware (Boston).

59 per cent are excessive and chain smokers. The results of the two control studies correspond closely to one another as well as to the results of study III (table 4).

The results in relation to the areas or hospitals where the cases were observed show uniformity. Small differences between the groups may well be explained on the basis of the small size of each series. The mountain state series includes 13 patients of Mormon faith. Mormons in general were found to smoke much less than our general hospital population. Among the Mormon patients with cancer of the lung, however, there was only 1 nonsmoker (72 years old). The others were long-time users of tobacco.

Comparing the three studies, we note little difference. For example, nonsmokers account for 0.0 per cent in control study I, 2.4 per cent in control study II and 1.4 per cent in study III. The percentage of heavy to chain smokers in these three groups is 88, 86.7 and 85.2 respectively, while the percentage of excessive and chain smokers totals 53, 59 and 49 respectively.

Since we thus have not been able to determine any essential difference in the amount of smoking in the three studies, we shall from here on refer to the total results of 605 cases.

Age Distribution.—The age distribution of cancer of the lungs in the present series shows 2.3 per cent of the patients to be under 40 years of age, while 79.3 per cent were 50 years or older (table 5). This distribution readily shows that it would be of little value to study the smoking habits of the younger age groups for the purpose of control studies, since in them, for reasons still unknown to us, cancer of the lungs is a rare phenomenon.

TABLE 3.—*Control Study II: Amount of Smoking in 83 Cases of Proved Cancer of the Lung as Determined by Investigators Using the Same Questionnaire as that Used in the Cases of this Study*

	Bellevue Hospital (Turner)	Boston City Hospital (Ware)	Crile Veterans Hospital (Surington)	Hines Veterans Hospital (Shabart)
Cases	22	16	15	30
Amount of Smoking:				
None	1	0	1	0
Light	2	0	0	1*
Moderately heavy	2	3	1	0
Heavy	6	2	6	9
Excessive	8	5	7	6
Chain	3	6	0	14

* Minimal smoker. (For definition see previous classification of smokers.)

Combined Data on Amount of Smoking.—The data on the amount of smoking among 605 patients with cancer of the lungs and 780 male patients with other diseases reflect the results of the individual studies reported. It may also be noted that there is no essential difference in the amount of smoking between the general hospital population and patients with diseases of the chest who do not have cancer. The total results show that whereas there are 14.6 per cent nonsmokers among the male general population there are 1.3 per cent nonsmokers among the male patients with cancer of the lungs; and while there are 54.7 per cent heavy to chain smokers and 19.1 per cent excessive and chain smokers among the general hospital group there are 86.4 and 51.2 per cent, respectively, among the patients with cancer. All these differences seem highly significant.

The results on the amount of smoking according to age groups (table 6) show that in general the patients with cancer of the lungs in their forties and early fifties have smoked more heavily than the older patients with this disease. This observation does not seem to apply to the few patients in their thirties. The age group 70 to 79 has the greatest percentage of light and moderately heavy smokers.

25. Eight of these cases were diagnosed in Dr. Papanicolaou's laboratory on conclusive evidence of carcinoma. One sputum and one pleural fluid examination were made at the Boston City Hospital.

The frequency of nonsmokers in the age groups shown for the patients without cancer is significantly different from that among patients with cancer in the same age groups. However, in the 30 to 39 age group the smoking habits of the patient with cancer are difficult to evaluate since too few patients of this age have been seen.

TABLE 4.—*Study III: Amount of Smoking Among Male Patients With Cancer of the Lung in Relation to Area or Hospital Where Cases Were Observed (Wynder)**

	Smoking Classification, %						
Areas or Hospitals	V	IV	III	II	I	0	Average Age
Barnes (76)	18.4	31.5	43.4	5.3	0.0	1.3	54.8
Los Angeles (50)	12.0	32.0	12.0	12.0	0.0	4.0	59.5
San Francisco (50)	20.0	28.0	36.0	14.0	2.0	0.0	54.9
Mountain states (50)	14.0	36.0	36.0	18.0	4.0†	2.0	60.1
St. Louis (25)	20.0	36.0	32.0	12.0	0.0	0.0	58.2
Eastern and northern states (50)	16.3	23.6	40.0	20.0	0.0	0.0	56.1
New York City (66)	20.0	40.0	32.3	7.7	0.0	0.0	55.8
Memorial Hospital (55)	23.6	27.3	29.1	10.9	5.5†	3.6	57.6
Total (422)	18.2	30.8	36.7	11.4	1.4	1.4	56.7

* This table does not include any cases represented in control studies I and II.
† Includes 1 minimal smoker.

TABLE 5.—*Age Distribution in 605 Cases of Cancer of the Lung in Men*

Age Groups	Percentage of Cases
30-39	2.3
40-49	17.4
50-59	42.6
60-69	30.9
70-79	6.8

TABLE 6.—*Percentage Distribution of Amount of Smoking in Respect to Age Groups Among 780 Men in the General Hospital Population and 605 Men with Cancer of the Lungs**

	Age Groups									
	30-39		40-49		50-59		60-69		70-79	
No. of Cases	(146)	(14)	(164)	(105)	(210)	(258)	(160)	(187)	(100)	(41)
Amount of smoking; class: 0	13.6	7.1	9.7	0.0	14.8	1.6	14.3	1.1	25.0	2.4
1	5.5	7.1	9.7	1.9	7.1	1.6	18.7	1.1	13.0	12.2
2	17.1	14.3	18.9	3.8	17.6	7.4	20.6	13.6	21.0	24.4
3	41.0	42.9	37.1	29.5	43.3	36.0	28.7	38.0	16.0	29.3
4	14.3	28.6	14.0	28.6	10.5	34.1	10.6	30.5	15.0	17.1
5	8.2	0.0	10.3	36.2	6.7	19.4	6.8	15.5	10.0	14.6

* The percentages for the general male hospital population are given in the left hand columns.

In comparing the amount of smoking among the various age groups, one must also consider the type of tobacco used, which has undergone a marked shift particularly when the youngest and oldest age groups are considered.

Statistical Analysis of Data.—The statistical analysis of these data has been carried out by Dr. Paul R. Rider, professor of mathematics at Washington University, and H. David Hartstein, M.A., instructor of statistics at Washington University.

On the assumption that smoking has no effect on the induction of cancer of the lungs, the probability (p) of a deviation from expectation as great or greater than that observed is as follows:

Control Study I: Class O, p is 0.0002; class O plus class I, p is 0.0002; classes 3 to 5 inclusive, p is 0.0226, class 4 plus class 5, p is 0.0002; class 4, p is 0.0046, and class 5, p is 0.0016.

Combined Results: The values for the combined results of 605 patients with cancer of the lung as compared with 780 men in the general hospital population are as follows: class O, class O plus class 1, classes 3 to 5 inclusive, class 4 plus class 5, class 4 and class 5 have p values which are in all cases less than 0.0001.

Their conclusion is as follows: "On the basis of the statistical data for both the control study I and the combined results, when the nonsmokers and the total of the high smoking classes of patients with lung cancer are compared with patients who have other diseases, we can reject the null hypothesis that smoking has no effect on the induction of cancer of the lungs. If smoking does not have anything to do with the induction of cancer of the lungs, then the observed deviation could occur only with the probability (p) as shown above."

Miscellaneous Data.—Nearly all (98.7 per cent) the cigaret smokers of the cancer group, but fewer pipe (62.5 per cent) and cigar (18 per cent) smokers, stated that they inhaled consciously. Seventy-eight and a half per cent of cancer patients interviewed stated that they usually began to smoke before breakfast.

Type of Tobacco: Among the general hospital population pipes and cigars were smoked most prominently

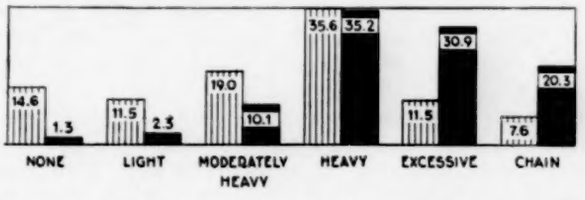

Fig. 3.—Percentages for amount of smoking among 605 male patients with cancer of the lungs (solid bars) and 780 men in the general hospital population without cancer (lined bars) with the same age and economic distribution.

in the older age groups. For example, only 4.3 per cent of the smokers in the age group 30 to 39 used chiefly pipes or cigars, 11.0 per cent in the age group 40 to 49, 12.9 per cent in the age group 50 to 59, 30 per cent in the age group 60 to 69 and 38 per cent in the age group 70 to 79. Only those patients were tabulated as either pipe or cigar smokers who smoked a given type of tobacco predominantly over the last twenty years of their smoking period. Among the age-adjusted general hospital population we find 12.4 per cent pipe smokers and 7.8 per cent cigar smokers and among the patients with cancer 4.0 per cent and 3.5 per cent respectively (fig. 4).

The average age of the pipe smokers with cancer of the lung was 60.5, with a range of 52 to 78, and the average age of the cigar smokers with cancer of the lung was 63.1, the range being from 53 to 76. The average number of pipes smoked by the cancer patients was 15.6 and the average number of cigars 6.8 per day for the last twenty years of their smoking history. This amount of smoking is decidedly higher than that found among the general cigar and pipe smokers.

Duration of Smoking: The duration of smoking in years dates to the first time the patient began smoking habitually to any degree. Of 605 patients with cancer in our series, 96.1 per cent had smoked for twenty years or more, 85.4 per cent for thirty years or more, 68.2 per cent for thirty-five years or more and 50.2 per

cent for forty years or more. One patient with epidermoid cancer began to smoke at 45 (20 cigarets a day), and clinical symptoms of cancer of the lungs developed at 50 (class I smoker). He had no other exposure to irritants. Only three of the patients with bronchiogenic cancer began to smoke after the age of 25 (fig. 5).

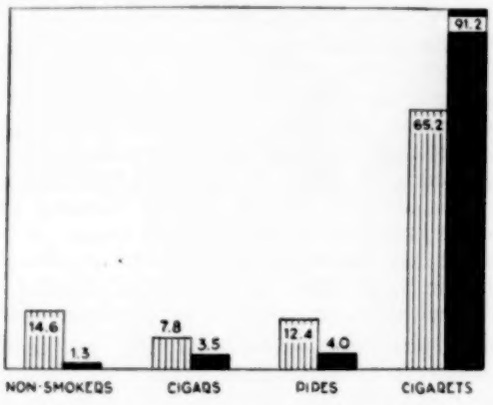

Fig. 4.—Smoking habits and type of tobacco smoked (in percentages) in 605 cases of cancer of the lungs (solid bars) and 780 men in the general hospital population (lined bars) with a similar age and economic distribution.

Adenocarcinoma in Men: Among 39 men[26] with adenocarcinoma there were 4 nonsmokers (10.3 per cent), a percentage higher than that found for the other types of bronchiogenic carcinoma. There were 7 chain smokers (18 per cent), significantly more than in the general male hospital population. Ten and three-tenths per cent were excessive, 38.5 per cent heavy, 15.4 per cent moderately heavy and 7.7 per cent light smokers. Among the latter there were 2 minimal smokers.

Data on Women:[27] Among 13 women with adenocarcinoma and 2 designated as having terminal bronchiolar carcinoma there was not 1 heavy smoker. Thirteen were nonsmokers and 2 light smokers. Among 25 patients with epidermoid and undifferentiated carcinoma, however, there were 15 smokers of many years' duration as well as 10 nonsmokers. Among those who smoked there were 1 light, 4 moderately heavy, 6 heavy, 2 excessive and 2 chain smokers.

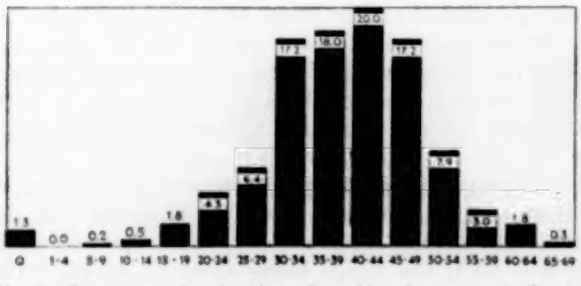

Fig. 5.—Percentages for duration of smoking in years, starting with the time when the patient first began to smoke habitually, in 605 cases of cancer of the lungs.

To determine the smoking habits among women in the general hospital population 552 patients without cancer of the lung have been interviewed at this hospital. The data resulting from this study show that but few women in the cancer age have been heavy smokers for many years and that most of the heavy smokers are young women. On the basis of our arbitrary smoking classification, we found 79.6 per cent of the women to be nonsmokers while 11.3 per cent were moderately heavy to chain smokers, and only 1.2 per cent of the controls in the cancer age[28] were excessive or chain smokers for at least twenty years (fig. 6).

COMMENT

Universal Increase.—If one feels that the greatly increased incidence of cancer of the lungs is real and that this increase is most marked in men, one may theorize that the change has been due to an external factor, or group of factors, nationally prevalent but applicable to men more and over a longer period than to women.

Influence of Tobacco.—Since in a small percentage of cases cancer of the lungs occurs in nonsmokers and minimal smokers and since it obviously does not develop in every person who has been a heavy smoker for a long time, it is apparent that smoking cannot be the only etiologic factor in the induction of the disease. From the evidence presented, however, the temptation is strong to incriminate excessive smoking, and in particular cigaret smoking, over a long period as at least one important factor in the striking increase of bronchiogenic carcinoma for the following reasons: (1) it

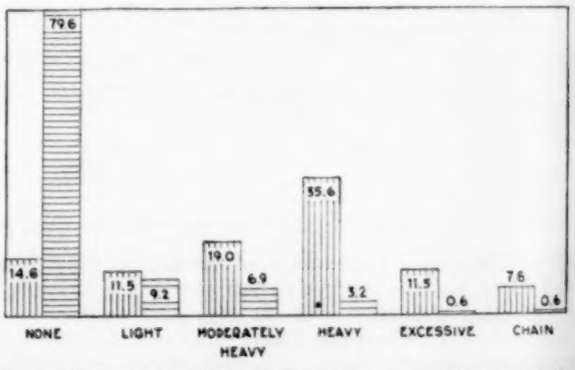

Fig. 6.—Amount of smoking in percentage among 780 male patients (vertically lined bars) and 552 female patients (horizontally lined bars) of the general hospital population with the same age and economic distribution as found among cases of cancer of the lungs.

is rare to find a case of epidermoid or undifferentiated carcinoma in a male patient who has not been at least a moderately heavy smoker for many years; (2) the use of cigarets is much greater among patients with cancer of the lungs than among other patients of the same age and economic groups; (3) the sex distribution of cancer of the lungs roughly corresponds to the ratio of long-term smoking habits of the two sexes (see section on "Duration of Smoking"); (4) the enormous increase in the sale of cigarets in this country approximately parallels the increase of bronchiogenic carcinoma.[29]

Amount of Smoking.—The data have clearly shown that the average patient with cancer of the lungs smokes much more heavily than the average patient of the same age and economic group with some other disease. This contrast becomes even greater if our observation of Mormons is considered, who as a group smoke far less than the general hospital population; Mormons with cancer of the lung were, with one exception, considerable smokers.

26. Includes 3 cases of Dr. C. T. Surington and 1 case of Dr. H. G. Turner.
27. Includes 4 cases of Dr. H. G. Turner and 3 cases of Dr. G. W. Ware.
28. See table 5.
29. It is taken for granted, of course, that by itself such parallelism would mean little since similar curves could be drawn for many other commodities.

The fact that patients with bronchiogenic cancer in their forties and fifties had smoked more heavily than those in whom the cancer developed at a later age may indicate that the greater the irritation the sooner will cancer develop in a susceptible person. Such an observation obviously does not apply to the individual case but rather to the age groups taken collectively. Too few patients below the age of 40 have been seen in order to evaluate this age group.

In general it appears that the less a person smokes the less are the chances of cancer of the lung developing and, conversely, the more heavily a person smokes the greater are his chances of becoming affected with this disease.

Type of Tobacco.—The majority of patients with cancer of the lungs are cigaret smokers rather than pipe or cigar smokers, the ratio being over and above that found in the general population. This fact may be due to one of the following reasons:

1. Cigaret smoke is more frequently inhaled than is that of either pipes or cigars. Obviously the lungs of an inhaler are exposed to a greater concentration of smoke than those of a person who does not consciously inhale.

2. Because of the greater physical and economic convenience, more persons are heavy smokers of cigarets than of either pipes or cigars. Among the latter one finds more minimal and light smokers than among the former.

3. Certain irritative substances may be present in cigarets in greater amounts than in pipes or cigars. The role of paper, the use of insecticides during the growth of the tobacco and other ingredients warrant further research in this regard.

Duration of Smoking.—One of the chief reasons many investigators have thought that tobacco has no effect on the development of cancer of the lungs has been their belief that women today smoke as much as men and that if tobacco plays a role the sex ratio of the disease should be about equal. The data presented demonstrate that it makes little difference how many women smoke today or have smoked for the past ten years, since results have shown that over 96 per cent of patients with cancer of the lungs have smoked for more than twenty years and that over 80 per cent have smoked for more than thirty years.

It is, of course, difficult to tell whether the important point in this regard is the fact that these persons have smoked for many years or that they have been heavy smokers for a brief period, because we have noted that also among the general male hospital population nearly all smokers have been smoking since their youth. For this reason it is difficult to evaluate the one case in our study in which the patient smoked only from his forty-fifth to his fiftieth year, at which time clinical signs of cancer developed. If one may judge from control data on women, it would appear that a long duration of smoking is at least one important factor in the induction of cancer of the lungs. The relatively low incidence of the condition in women might be explained by the fact that few women in the cancer age have smoked for an extensive period.

On the basis of a twenty year period of smoking, it may be of interest to note that, while only 1.2 per cent of the women were excessive or chain smokers, by contrast 19.1 per cent of the male controls were in those smoking groups, a ratio which points in the same direction as the sex ratio of lung cancer.

Lag Period.—If smoking is to be regarded as an important etiologic factor in the development of cancer of the lungs, apparently a time lag exists for this disease as well as for carcinoma of the bladder, known to occur years after cessation of exposure to aniline. We have now seen 3 cases in which clinical signs of cancer of the lung appeared ten years or more after the patient stopped smoking. The 3 patients had smoked for thirty years or more, and none gave a history of occupational or other irritative exposures. Two of them had stopped smoking because of a bothersome chronic cough and 1 because of concomitant heart disease. In 1 of the patients, a 67 year old warehouse clerk, clinical symptoms of cancer developed thirteen years after the cessation of smoking. The phenomenon of the lag period is of course well known in cancer research.

Adenocarcinoma in Men.—Since the great increase in cancer of the lungs has mostly involved the epidermoid and undifferentiated carcinomas, it would appear that the exogenous factors possibly affecting these types of cancer play a lesser role, if any, in the induction of adenocarcinomas of the lung in men. As yet we have not seen a sufficient number of cases of this type of cancer to warrant definitive conclusions. It appears, however, that on the basis of present data one is more likely to find nonsmokers or minimal smokers with this type of cancer than with the other types. At the same time, however, the percentage of chain smokers among men with adenocarcinomas of the lung is greater than among the general hospital population. It seems, therefore, that tobacco smoke has also some influence on the induction of adenocarcinoma in men, even though, as judged from the incidence, the influence on this type is much less marked than on the other types of bronchiogenic carcinoma.

Cancer of the Lungs in Women.—Many observers have commented on the fact that bronchiogenic carcinoma, while on the increase among both men and women, is increasing more rapidly among men. In 100 consecutive cases collected by Lindskog [30] in 1938 to 1943 the ratio was 4.5 to 1, and in another series collected in 1947 and 1948 the ratio had reached 24 to 1.[31] At Barnes Hospital the ratio in our last 150 cases has been 18.5 to 1. This shift in ratio has been noted in varying proportions throughout the country. Such a radical change warrants a careful analysis.

The insufficient number of cases of cancer of the lungs in women in our survey does not allow definite conclusions at this time. So far, however, smoking seems to have had no apparent effect on the incidence of adenocarcinoma in women. It is of great interest that we have observed 10 cases of epidermoid and undifferentiated carcinoma of the lungs of women who were nonsmokers with no history of occupational or other irritative exposure. This percentage of nonsmokers in women with cancer of the lung is much higher than that found among men. Proper explanations for this finding remains to be advanced. At the same time it appears strongly suggestive that heavy smoking plays a significant role in the induction of epidermoid and undifferentiated carcinoma of the lungs in women, since the percentage of heavy smokers is considerably higher in the cancer group than in the general hospital control group.

30. Lindskog, G. F.: Bronchiogenic Carcinoma, Ann. Surg. **124**: 667-674 (Oct.) 1946.

31. Lindskog, G. F., and Bloomer, W. D.: Bronchiogenic Carcinoma, Cancer **1**: 234-237 (July) 1948.

CONCLUSION AND SUMMARY

1. Excessive and prolonged use of tobacco, especially cigarets, seems to be an important factor in the induction of bronchiogenic carcinoma.

2. Among 605 men with bronchiogenic carcinoma, other than adenocarcinoma, 96.5 per cent were moderately heavy to chain smokers for many years, compared with 73.7 per cent among the general male hospital population without cancer. Among the cancer group 51.2 per cent were excessive or chain smokers compared to 19.1 per cent in the general hospital group without cancer.

3. The occurrence of carcinoma of the lung in a male nonsmoker or minimal smoker is a rare phenomenon (2.0 per cent).

4. Tobacco seems at this time to play a similar but somewhat less evident role in the induction of epidermoid and undifferentiated carcinoma in women. Among this group a greater percentage of nonsmokers will be found than among the men, with 10 of 25 being nonsmokers.

5. Ninety-six and one-tenth per cent of patients with cancer of the lungs who had a history of smoking had smoked for over twenty years. Few women have smoked for such a length of time, and this is believed to be one of the reasons for the greater incidence of the disease among men today.

6. There may be a lag period of ten years or more between the cessation of smoking tobacco and the occurrence of clinical symptoms of cancer.

7. Ninety-four and one-tenth per cent of male patients with cancer of the lungs were found to be cigaret smokers, 4.0 per cent pipe smokers and 3.5 per cent cigar smokers. This prevalence of cigaret smoking is greater than among the general hospital population of the same age group. The greater practice of inhalation among cigaret smokers is believed to be a factor in the increased incidence of the disease.

8. The influence of tobacco on the development of adenocarcinoma seems much less than on the other types of bronchiogenic carcinoma.

9. Three independent studies have resulted in data so uniform that one may deduce the same conclusions from each of them.

ADDENDUM

Since the data presented in this paper were tabulated, 45 additional interviews of male patients with epidermoid or undifferentiated cancer of the lung have been obtained. Eight of these patients have been interviewed by Dr. J. L. Ehrenhaft from the University of Iowa Hospital, 9 were given our questionnaire by Lt. Col. J. M. Salyer from Fitzsimons General Hospital and 7 were reported on by Dr. E. J. Shabart from the Veterans Administration Hospital, Hines, Ill. Among these 24 cases there were no nonsmokers or light smokers, 7 heavy smokers, 13 excessive smokers and 4 chain smokers. Twenty-one additional patients have been interviewed by Miss Croninger on the Barnes Hospital Chest Service. Among these there were 1 nonsmoker (a 72 year old blacksmith), 10 heavy smokers, 6 excessive smokers and 4 chain smokers. These 45 cases, which include reports independently made at two additional centers (University of Iowa and Fitzsimons General Hospital), show the same trend noted in the larger series.

CANCER AND TOBACCO SMOKING

A Preliminary Report

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and
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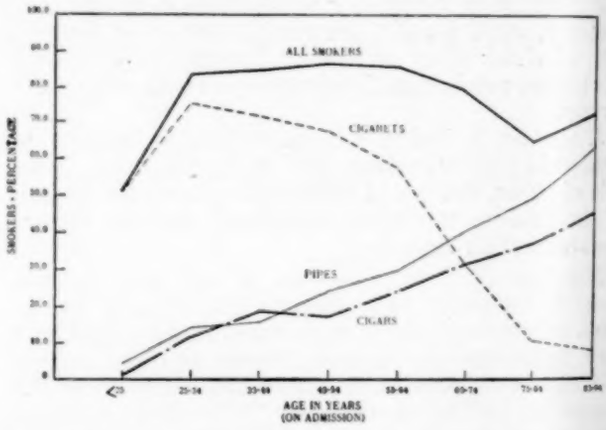
The published literature on use of tobacco and its possible association with human cancer fails to show clearcut consistent observations. Reviews of the literature for the past twenty years reveals that it is often conflicting and that it consists for the most part of studies which are inconclusive because of lack of adequate samples, lack of random selection, lack of proper controls or failure to age-standardize the data. Potter and Tully[1] have reported a higher proportion of smokers in patients with cancer of the "buccal cavity" and "respiratory tract" among males "over the age of 40" who were seen at Massachusetts cancer clinics.

Since 1938 a history of tobacco usage has been obtained routinely from all patients admitted to the Roswell Park Memorial Institute, Buffalo. These histories are part of the regular clinical history and are taken before the final diagnosis has been established. This procedure is considered especially important from the standpoint of excluding bias. Approximately half the patients admitted to the institute are subsequently found not to have cancer. Special attention with respect to the history of smoking has not been paid to any single group of conditions, so that these records may be presumed to be free from bias which might result from preconceived ideas as to relation between smoking and a particular form of cancer.



Percentage of patients who had ever smoked by type of smoking.

The histories record the date smoking began, duration, type of smoking and amount per day. The reliability of the quantitative aspects of smoking obtained by a history is of course highly variable. It is presumed, however, that such errors are not selective with respect to presence or absence of cancer, especially since only patients suspected by their physicians of having cancer are admitted to the Institute.

With technical assistance of Elizabeth Brezee and David Robbins.
From the Bureau of Cancer Control, Division of Medical Services, New York State Department of Health.
Dr. Louis C. Kress, Dr. Joseph G. Hoffman and Miss Olive C. Ralston, of the staff of the Roswell Park Memorial Institute, assisted by making available the records of the institute and by making suggestions as to the planning of the study.

1. Potter, E. A., and Tully, M. R.: The Statistical Approach to the Cancer Problem in Massachusetts, Am. J. Pub. Health 35: 485-490, 1945.

This report is based on a study of 1,045 male cancer patients and 605 male noncancer patients. The cancer sites selected were lung, lip, pharynx, esophagus, colon, rectum and a scattered number of other sites. The noncancer patients were those with symptoms referable to the same sites but which proved not to be due to cancer. Only the users of cigarets, pipes and cigars are considered here, since the number of patients who used snuff or chewing tobacco was negligible. Smokers engaging in more than one form of smoking entered into separate analysis for each such form, so that the sum of smokers is less than the sum of smokers of each type. The factor studied was whether or not the patient had ever smoked, regardless of whether he was a smoker at the time of admission.

Over 80 per cent of all patients were smokers (table 1). Prevalence of smokers, regardless of type, did not vary strikingly with age past the age of 25 (see the accompanying figure). Prevalence of cigaret smokers, however, decreased with age, and that of pipe smokers and cigar smokers increased with age. Obviously, comparison of groups with differing age composition would show different proportions of cigaret, pipe and cigar smokers because of this factor alone. Accordingly, comparisons should be made of age-specific prevalence rates or of prevalence rates standardized for age

TABLE 1.—*Prevalence of Smokers Among Male Cancer and Noncancer Patients by Type of Smoking*

	No. of Cases	Percentage of Smokers *			
		All Types	Cigarets	Pipes	Cigars
Cancer	1,045	84.8	56.0	30.3	22.4
Noncancer	605	77.8	46.0	24.3	20.8
P †	.....	0.01	0.01	0.01	0.47

* Age standardized.
† P denotes probability here and in tables 2 and 3.

by applying the age-specific rates to a standard population. The latter device was adopted, using the entire series of 1,650 patients as the standard population.

The significant observations are summarized in tables 1, 2, 3, 4 and 5. There were more smokers among cancer patients than noncancer patients, because of an excess of cigaret and pipe smokers among the former (table 1). This excess was due entirely to the increased percentage of cigaret smokers among patients with cancer of the lung and the increased percentage of pipe smokers among patients with cancer of the lip (table 2). These differences, in turn, were confined to those who had smoked cigarets or pipes for twenty-five years or longer (table 3).

It should be noted that the prevalence rates of smokers in columns 2 and 4 of table 3 are age-standardized rates, obtained by applying the age-specific rates for each subgroup to the age distribution of the total group of 1,650 male patients. Since length of smoking is related to age, this statistical procedure was necessary to exclude the possibility that the greater percentage of "25 years or more" smokers in the cancer groups was due solely to the greater proportion of older persons in these groups. The failure to find comparable differences in smokers of less than twenty-five years' duration may be due to the relatively small percentage of such smokers which may be expected in an older population. Further study of large numbers of younger patients may alter this observation.

In tables 4 and 5 the data are presented to show the relative prevalence of lung and lip cancer among nonsmokers and among cigaret, pipe and cigar smokers in the patient population. There were more than twice as many cases of lung cancer among cigaret smokers as among any other group. Pipe smokers and cigar

TABLE 2.—*Prevalence of Smokers Among Male Patients by Type of Smoking and Diagnostic Group*

Diagnosis	No. of Cases	Percentage of Smokers *							
		Any Type (1)		Cigaret (2)		Pipes (3)		Cigars (4)	
		%	P	%	P	%	P	%	P
Lung cancer compared with—	236	84.7	....	66.1	....	13.5	....	11.2	....
Other cancer (except lip)	666	82.9	0.53	48.0	0.01	25.8	0.01	20.3	0.01
Lung nontumors	124	81.1	0.39	53.1	0.02	25.5	0.09	13.4	0.64
Other noncancer	481	78.3	0.03	44.1	0.01	25.3	0.01	22.7	0.01
Lip cancer compared with—	143	84.5	....	45.3	....	48.1	....	26.5	....
Other cancer (except lung)	666	82.9	0.58	48.0	0.48	25.8	0.01	20.3	0.11
Lip nontumors	51	74.0	0.09	43.0	0.78	30.7	0.02	34.9	0.22
Other noncancer	554	78.1	0.23	46.4	0.81	23.8	0.01	19.6	0.08

* Age standardized.

smokers had no more cancer of the lung than did nonsmokers. Lip cancer was significantly increased among pipe smokers but not among cigaret smokers. Cases of lip cancer were increased also among cigar smokers.

In table 4 persons who smoked more than one type of tobacco are counted in each category. In table 5 only those who smoked but one type of tobacco are considered. The observations in table 4 with respect to lung cancer are the same as in table 5, i. e., only cigaret smokers show any significant increase of lung cancer over nonsmokers. For lip cancer, only pipe smokers show a significant increase over nonsmokers.

No other site of cancer that was included in this study was found to be associated with any particular type of smoking. However, not all sites of cancer were

TABLE 3.—*Prevalence* of Cigaret and Pipe Smokers Among Male Patients by Duration of Smoking and Diagnostic Group*

Diagnosis	No. of Cases	Duration of Smoking					
		Under 25 Yr.			25 Yr. and Over		
		(1) No.	(2) % *	P	(3) No.	(4) % *	P
Cigaret Smokers							
Lung cancer compared with—	236	25	11.7	....	148	54.1	....
Other cancer (except lung and lip)	666	74	13.0	0.62	233	34.9	0.01
Lung nontumors	124	19	16.3	0.23	54	36.9	0.01
Other noncancer	481	92	14.3	0.34	128	29.8	0.01
Pipe Smokers							
Lip cancer compared with—	143	8	7.8	....	60	35.7	....
Other cancer (except lung and lip)	666	26	3.9	0.02	162	22.9	0.01
Lip nontumors	51	5	10.6	0.35	11	21.5	0.04
Other noncancer	554	35	5.8	0.24	87	17.9	0.01

* Age standardized.

studied. It is planned to continue analysis of the records of the Roswell Park Memorial Institute to provide data regarding all types of malignant tumors.

These data indicate that, in a hospital population, cancer of the lung occurs more than twice as frequently among those who have smoked cigarets for twenty-five years than among other smokers or nonsmokers of comparable age. Pipe smokers apparently experience

an almost equal increase in the incidence of lip cancer, compared with other smokers or nonsmokers. It is somewhat surprising to find that the type of smoking, i. e., cigarets for lung cancer, pipe for lip cancer, is the associated factor, rather than the actual use of tobacco.

The data suggest, although they do not establish, a causal relation between cigaret and pipe smoking and cancer of the lung and lip, respectively. The statistical association may, of course, be due to some other unidentified common factor between these types of smoking and lung and lip cancer. Cancer is now generally considered a disease attributable to multiple causative factors. Among these are "irritants." The generalization has been advanced [2] that, although not all irritants are carcinogenic, all carcinogens are irritants, that is, capable of inducing chronic reparative hyperplasia. Berenblum [2a] has shown also that an irritant (croton resin; basic tar fraction) which is noncarcinogenic alone may nevertheless increase the percentage of tumors produced when its action is combined with that of a carcinogen. Thus, some experimental basis exists for explaining the apparent effect of cigaret and pipe smoking, although the true nature of the association with lung and lip cancer remains to be determined.

TABLE 4.—*Comparison of the Proportion* of Cases of Lung and Lip Cancer Among Male Nonsmokers and Smokers of 25 Years' Duration or More at Roswell Park Memorial Institute, 1938-1948*

	No. of Persons	Lung Cancer			Lip Cancer		
		Cases	Rate*	P†	Cases	Rate*	P†
Nonsmokers compared with:	293	23	8.6	....	20	6.9	....
Cigaret smokers ‡.....	600	148	20.7	0.01	37	5.9	0.55
Pipe smokers ‡.....	333	33	8.6	1.00	60	13.4	0.01
Cigar smokers ‡.....	363	22	8.5	0.97	39	12.5	0.03

* Standardized for age against age distribution of total males.

† Probability of the observed difference between smokers and nonsmokers occurring by chance alone.

‡ Multiple smokers, e. g., persons smoking more than one type of tobacco plus those smoking only one type.

TABLE 5.—*Comparison of the Proportion* of Cases of Lung and Lip Cancer Among Male Nonsmokers and Smokers of 25 Years' Duration or More at Roswell Park Memorial Institute, 1938-1948*

	No. of Persons	Lung Cancer			Lip Cancer		
		Cases	Rate*	P†	Cases	Rate*	P†
Nonsmokers compared with:	293	23	8.6	....	20	6.9	....
All smokers ‡.....	761	148	17.1	0.01	73	8.9	0.29
Cigaret smokers ‡.....	479	115	20.9	0.01	22	5.1	0.29
Pipe smokers ‡.....	166	19	10.6	0.48	34	15.7	0.01
Cigar smokers ‡.....	116	14	12.8	0.18	17	11.6	0.13

* Standardized for age against age distribution of total males.

† Probability of the observed difference between smokers and nonsmokers occurring by chance alone.

‡ Persons smoking only one type of tobacco.

2. (*a*) Berenblum, I.: Irritation and Carcinogenesis, Arch. Path. **38:** 233-244 (Oct.) 1944. (*b*) Pullinger, B. D.: First Effect on Mouse Skin of Some Polycyclic Hydrocarbons, J. Path. & Bact. **50:** 463-471, 1940.

Safeguarding the Profession.—Every physician should aid in safeguarding the profession against admission to it of those who are deficient in moral character or education.—Section 3, Chapter III of the PRINCIPLES OF MEDICAL ETHICS of the American Medical Association.

EPINEPHRINE, PREGNENOLONE AND TESTOSTERONE IN THE TREATMENT OF RHEUMATOID ARTHRITIS

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Reports of the effectiveness of cortisone (Kendall's compound E, or 17-hydroxy-11-dehydrocorticosterone) and of pituitary adrenocorticotropic hormone (ACTH) in the treatment of rheumatoid arthritis and spondylitis [1] have given rise to the hope that substances known to stimulate endogenous production or liberation of pituitary adrenocorticotropic hormone might also be effective in these conditions. Vogt [2] demonstrated in several different species of animals that the amount of active cortical material released into the suprarenal vein in one minute is many times that which can be extracted from both adrenal cortices by present methods. The administration of epinephrine was found to increase the amount of cortical material which could be recovered from suprarenal venous blood by several hundred per cent.[3] Her results suggested that epinephrine, administered in doses approaching the amounts that might be liberated normally within the body, stimulates the adrenal cortex directly. Long [4] concluded that the action of epinephrine on the adrenal cortex is indirect and is dependent on the presence of the anterior pituitary gland. Thorn [5] has emphasized the fact that epinephrine is effective in stimulating the pituitary-adrenal system in man. He and his collaborators [6] showed that epinephrine increases 11-oxysteroid and 17-ketosteroid excretion and lowers the total circulating eosinophil count by 50 per cent or more in normal subjects but not in those with pituitary or adrenocortical insufficiency. Almy and Laragh [7] confirmed the observation that epinephrine consistently produces eosinopenia in normal persons. Thorn [8] suggested using 0.5 mg. of epinephrine subcutaneously every six hours in patients with rheumatoid arthritis and referred to improvement which he had obtained in

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7. Almy, T. P., and Laragh, J. H.: Reduction in Circulating Eosinophils Following Epinephrin, Insulin and Surgical Operations, Am. J. Med. **6:** 507, 1949.

8. Thorn, G. W., In discussion on Hench, P. S.; Kendall, E. C.; Slocumb, C. H., and Polley, H. F.: Effect of a Hormone of the Adrenal Cortex (17-Hydroxy-11-Dehydrocorticosterone: Compound E) and of the Pituitary Adrenocorticotropic Hormone on Rheumatoid Arthritis, read before the Sixty-Second Annual Meeting of the Association of American Physicians, Atlantic City, N. J., May 3, 1949.

patients given such treatment. However, he and his collaborators [6] subsequently stated that after repeated administration of epinephrine the drug loses its effectiveness as an adrenal cortical stimulator. Nevertheless, these investigators have reaffirmed "very slight but definite improvement" in 2 patients with rheumatoid arthritis treated by repeated injections of epinephrine.[6] They also noted that in a small number of patients with rheumatoid arthritis significant eosinopenia does not develop after the administration of epinephrine and that 1 patient in whom eosinopenia did not develop after pituitary adrenocorticotropic hormone therapy proved refractory to treatment with this agent.

Other agents of a hormonal nature have also been suggested as of possible value in the treatment of the rheumatoid state. Among these are pregnenolone and testosterone propionate. Pregnenolone is the 3-hydroxy analogue of progesterone, occurring as a penultimate stage in the oxidative preparation of the latter.[9] It has been demonstrated by Hoagland [10] that the administration of pregnenolone brings about a reduction in the urinary excretion of 17-ketosteroids under conditions of stress. This fact prompted Davison and Koets [11] to use the agent in the treatment of rheumatoid spondylitis because it had been observed [12] that the excretion of 17-ketosteroids is increased in this disease. Pregnenolone acetate in oil was administered by intramuscular injection to patients with active rheumatoid spondylitis. A decrease in urinary 17-ketosteroid excretion as well as objective and subjective improvement was reported to have occurred. Ishmael and associates [13] have reported that pregnenolone acetate is an effective treatment for rheumatoid arthritis. It was used alone and in combination with testosterone propionate. When it was used alone it was not considered as effective in controlling the rheumatoid state except in 4 patients (of 90 treated). Other workers [14] likewise have reported improvement in relatively small numbers of patients treated with this agent. Henderson, Weinberg and Wright,[9] in reviewing these reports, concluded that more than 50 per cent of patients receiving pregnenolone show symptomatic improvement, that the drug is of low toxicity and that it produces "the nonspecific sense of well-being that is characteristic of treatment with estradiol or testosterone."

Ishmael and his group [13] have also reported that of 90 patients with rheumatoid arthritis who were treated with 100 to 300 mg. daily of testosterone propionate intramuscularly, approximately 65 per cent showed decided improvement within twenty-four hours. Testosterone, estradiol benzoate and pregnenolone in various combinations induced remissions in 81 of 90 patients who were treated and "only five . . . did not respond adequately." These results are particularly remarkable because it has been suggested [15] that testosterone depletes the adrenal cortex of steroids and decreases 11-oxysteroid excretion. This, of course, is the reverse of the effect produced by cortisone and pituitary adrenocorticotropic hormone on 11-oxysteroid urinary excretion. Furthermore, Hench [16] has commented on the almost universal failure of estrogens in the treatment of rheumatoid arthritis.

The present study has been concerned with the effects of epinephrine, pregnenolone and testosterone propionate on patients with rheumatoid arthritis. Thorn and others [6] stated that the fall in circulating eosinophils is the most sensitive indicator of adrenal cortical activation. In this study eosinophil counts were frequently performed before, during and after treatment with epinephrine and pregnenolone in order to determine their possible effect on, or stimulation of, adrenal cortical activity as measured by this index. A detailed study of the eosinophil level was performed on 1 patient receiving testosterone propionate in oil.

TABLE 1.—*Representative Type of Observations Made on Patients with Peripheral Rheumatoid Arthritis While They Were Receiving Treatment**

Date		10/7	10/10	10/12	10/13	10/14	10/19	10/25
Knees								
Circumference at midpatellar level in cm.	Rt.	38.5	39.0	39.0	39.0	38.5	37.5	37.5
	Lt.	38.0	38.5	38.0	38.5	38.5	37.0	37.0
Heat	Rt.	+	+	+	+	+	+	+
	Lt.	+	+	+	+	+	+	+
Redness	Rt.	0	0	0	0	0	0	0
	Lt.	0	0	0	0	0	0	0
Tenderness †	Rt.	4+	4+	3+	4+	4+	2+	3+
	Lt.	4+	4+	3+	4+	4+	2+	3+
Flexion, degrees	Rt.	100	...	90	100	110	90	80
	Lt.	120	...	90	120	110	90	80
Extension, degrees	Rt.	135	...	160	135	160	150	155
	Lt.	135	...	160	135	150	150	160
Ankles								
Circumference at level of lateral malleolus in cm.	Rt.	26.0	28.0	26.25	25.0	...	27.0	26.0
	Lt.	25.0	25.5	26.5	26.0	...	27.0	26.0
Heat	Rt.	+	+	+	+	...	+	+
	Lt.	+	+	+	+	...	+	+
Redness	Rt.	0	0	0	0	...	0	0
	Lt.	0	0	0	0	...	0	0
Tenderness †	Rt.	2+	3+	2+	3+	2+	3+	2+
	Lt.	1+	2+	2+	2+	2+	0	0
Dorsiflexion, degrees	Rt.	90	...	75	85	...	75	80
	Lt.	90	...	75	90	...	70	70
Plantar flexion, degrees.	Rt.	160	...	160	160	...	170	135
	Lt.	170	...	170	160	...	170	150
Wrists								
Circumference at radial styloid in cm.	Rt.	17.0	...	17.0	17.0	...	17.0	16.5
	Lt.	16.5	...	16.5	17.0	...	16.5	16.75
Heat	Rt.	0	...	+—	+—	...	0	+
	Lt.	0	...	+	+	...	+	+
Redness	Rt.	0	...	0	0	...	0	0
	Lt.	0	...	0	0	...	0	0
Tenderness †	Rt.	1+	...	2+	3+	...	0	3+
	Lt.	1+	...	2+	3+	...	1+	3+
Ventroflexion, degrees	Rt.	120	...	120	135	...	110	110
	Lt.	120	...	120	120	...	120	120
Dorsiflexion, degrees	Rt.	135	...	135	135	...	135	135
	Lt.	135	...	135	135	...	135	135
Subjective		...	...	Good	Bad	Fair	Bad	Fair

* Treatment of patient G with pregnenolone, 300 mg. daily, started Oct. 9, 1949 and ended Oct. 16, 1949.

† Here and on table 2, tenderness is classified: 1+, patient admits tenderness; 2+, grimaces during palpation; 3+, withdraws from palpation, and 4+, has violent emotional reaction (crying, rage) with palpation.

MATERIALS AND METHODS

All patients who were studied had clinical and roentgenographic evidence of peripheral rheumatoid arthritis and/or spondylitis. They were selected from patients hospitalized at the Veterans Hospital, the Bronx, New

9. Henderson, E.; Weinberg, M., and Wright, W. A.: Pregnenolone, from the Division of Clinical Research, Schering Corporation, Bloomfield, N. J., to be published.

10. Hoagland, H.: Adventures in Biological Engineering, Science **100**: 63, 1944.

11. Davison, R. A., and Koets, P.: The Effect of Δ 5-Pregnenolone on Urinary 17-Ketosteroid Excretion and Symptomatology of Ankylosing Spondylarthritis, with a Note on the Results of Fractionation, Seventh International Congress on Rheumatic Diseases, New York, May 30-June 3, 1949.

12. Davison, R. A.; Koets, P., and Kuzell, W. C.: Excretion of 17-Ketosteroids in Ankylosing Spondylarthritis and in Rheumatoid Arthritis: A Preliminary Report, J. Clin. Endocrinol. **7**: 201, 1947.

13. Ishmael, W. K.; Hellbaum, A.; Kuhn, J. F., and Duffy, M.: The Effects of Certain Steroid Compounds on Various Manifestations of Rheumatoid Arthritis, J. Oklahoma M. A. **42**: 434, 1949.

14. Personal communication to Henderson, Weinberg and Wright.[9]

15. Albright, F.: Osteoporosis, Ann. Int. Med. **27**: 861, 1947.

16. Hench, P. S.: The Potential Reversibility of Rheumatoid Arthritis, Proc. Staff Meet. Mayo Clin. **24**: 167, 1949.

York, from ambulatory patients treated at the Arthritis Clinic of the New York Hospital and from private practice. Inasmuch as a certain number of patients with rheumatoid arthritis in the early stages of the disease may improve spontaneously, only patients showing a chronic but active course of the disease were selected for treatment. Activity was judged by the presence of a combination of several of the following conditions: heat, redness, soft tissue swelling, joint immobility, joint effusion, pain, tenderness, the "jelling phenomenon" of Hench, fever, leukocytosis and elevated sedimentation rate.

TABLE 2.—*Representative Type of Observations Made on Patients with Rheumatoid Spondylitis While They Were Receiving Treatment* *

Date	9/17	9/20	9/27	9/30	10/3	10/10	10/19	10/21	10/25	10/28	10/31	11/3	11/7	11/9	11/21	11/29
Neck																
Torticollis to left, degrees	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20
Tenderness,† bilateral	2+	2+	2+	1+	1+	1+	1+	1+	1+‡	1to2+	1+‡	1+	2+	1+	1+	2+
Extension, degrees	0	0	0	0	0	—	0	0	0	0	10	10	10	15	30	15
Lateral flexion § in inches Rt.	1½	1⅜	1	1	⅞	—	—	1	½	1	½	1½	1½	2½	2	1¾
Lt.	1	¾	⅝	¾	¾	—	—	¾	1	¾	½	1¼	1	1¼	½	1¼
Rotation ‖ in inches Rt.	½	⅝	⅛	⅜	½	—	0	½	¾	¾	⅞	½	⅞	½	1	¾
Lt.	¾	½	⅝	½	½	—	½	½	½	½	½	½	½	½	½	1
Chest																
Maximum expansion at nipple line	1½	1⅞	2¼	2	2¼	1½	1¼	1½	1¾	1½	2⅜	2⅛	2⅛	1¾	1½	1½
Back																
Muscle spasm	+	+	+	+	+	+	..	+	+	+	+	+	+	+	+	+
Flattening of lumbar curve	+	+	+	+	+	+	..	+	+	+	+	+	+	+	+	+
Tenderness † of dorsal region of spine ¶	L5 down 2+	L1 down 2+	L5 down 2+	T12 down 1+	T8 down 1+	T10 down 1+	T6 3+; S 1+	T5 to 11, 1+	T5 & 6, 1+; S 1+	T12 down 1+	S 1+	T8 down 1+	T3 to 7, 2+; S 1+	S 1+	..	..
Ventroflexion # of spine	16¾	15	16¾	14½	14	14¾	14¾	13	10	8¾	6	4	8	6	3½	5
Lateral flexion of spine ** Rt.	2⅝	2¼	2½	2½	2¼	—	2	3	3¾	3½	3½	4	2¾	3	2½	..
Lt.	2½	3½	2½	2	2¼	—	2	2½	3	3¼	3	3	2	2¾	2½	2¾
Shoulders																
Tenderness † Rt.	1+	1+	0	—	0	—	—	0	0	2+	0	0	0	0	2+	2+
Lt.	1+	0	0	—	0	—	—	0	0	0	0	0	0	0	1+	2+
Abduction in degrees above horizontal plane Rt.	10	10	10	—	10	—	—	—	—	10	30	45	10	45	—	15
Lt.	10	15	15	—	15	—	—	—	—	45	45	45	45	40	—	30
Internal †† rotation Rt.	L2	T12	T10	—	T10	—	—	—	—	T12	T10	T8	T8	T8	T11	T12
Lt.	L2	T12	T10	—	T10	—	—	—	—	T10	T8	T7	T7	T8	T10	T8
Erythrocyte sedimentation rate (Cutler) (23 on July 22)	19							18				20	19			

* Treatment of patient D with epinephrine, 0.5 mg. subcutaneously every six hours, began Sept. 21, 1949 and ended Oct. 10, 1949. Pregnenolone acetate therapy, 300 mg. daily by the intramuscular route for twenty-two days, a total dose of 6,600 mg., began Oct. 19, 1949 and ended Nov. 9, 1949. Ventroflexion of the neck, tested on each of the dates listed, was always chin to chest.

† Tenderness classified as on table 1.

‡ On October 25 and 31 tenderness of neck was on the left only.

§ Lateral flexion of neck is the maximum change in the distance between the root of the tragus and the acromioclavicular joint.

‖ Rotation of the neck is the maximum change in the distance between the cleft of the chin and the acromioclavicular joint.

¶ L indicates lumbar and T, thoracic vertebrae; S indicates sacral region.

Ventroflexion of spine is measured as the shortest distance in inches between the most dependent finger tip and the floor (with the knees fixed in extension).

** Lateral flexion of spine is measured as the maximum change in distance between the most dependent finger tip and the floor during movement from the erect position.

†† Internal rotation of shoulder is measured as that spinous process able to be touched by the flexed second metacarpophalangeal joint when elbows, wrists and hands are normal. L indicates lumbar and T thoracic vertebrae.

All patients were observed for a control period of at least two weeks prior to institution of therapy. Patients were studied at frequent intervals with respect to appearance, measurements, mobility and tenderness of the affected joints. Tables 1 and 2 illustrate the type of observation made on these patients during this study. Eosinophil counts were performed by two of us (C. M. G. and S. A. B.) according to the modification by Forsham and associates[17] of the direct method of Dunger. Serial sedimentation rates were obtained on all patients.

17. Forsham, P. H.; Thorn, G. W.; Prunty, F. T. G., and Hills, A. G.: Clinical Studies with Pituitary Adrenocorticotropin, J. Clin. Endocrinol. 8: 14, 1948.

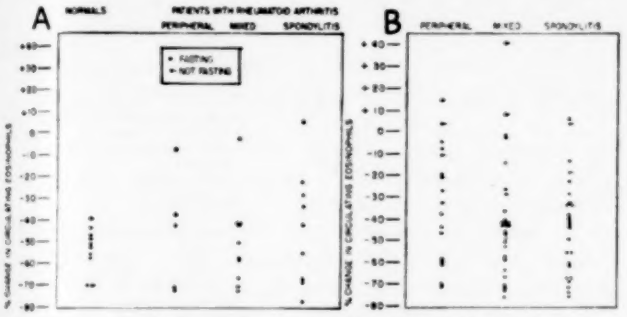
RESPONSE OF CIRCULATING EOSINOPHILS TO EPINEPHRINE IN RHEUMATOID ARTHRITIS

Blood for the control eosinophil counts was obtained at 8:30 a. m. This was followed immediately by the subcutaneous injection of 1.5 mg. of epinephrine in each patient. A second eosinophil count was performed four hours later. In the majority of instances the subjects fasted until after the second blood sample was drawn.

The epinephrine test was performed on 10 healthy young physicians who served as normal controls (part *A* of the accompanying illustration). Four hours after the injection of epinephrine all of them responded with a fall in circulating eosinophils of 40 per cent or more. This was selected as a significant value.

The response to initial injections of epinephrine in 24 fasting patients with rheumatoid arthritis is also shown in part *B* of the accompanying illustration. Seven had an insignificant response (less than 40 per cent fall) on the initial test. Results after subsequent injections of epinephrine often differed from the initial response without regard to whether or not the patient was fasting. The results of a total of 70 tests on the 24 patients are plotted in part *B*. Sixteen of these patients were not treated with epinephrine. The remaining 8 had not

received recent injections of epinephrine prior to these tests. There was an inadequate response in 28 of the 70 tests (40 per cent). The nature of the responses in 16 patients who had two or more tests performed is shown in table 3. Three of these never had significant eosinopenia following epinephrine, while 6 displayed an inconstant response. Seven patients consistently



Response of circulating eosinophils to epinephrine (*A*) four hours after the initial administration of 0.5 mg. of the drug subcutaneously in 10 normal controls and in 24 patients with rheumatoid arthritis; (*B*) in a total of seventy tests made four hours after the administration of 0.5 mg. of the drug subcutaneously to 24 patients with rheumatoid arthritis.

manifested a significant fall in circulating eosinophils after receiving epinephrine. One patient in whom eosinopenia never developed following 0.5 mg. of epinephrine given subcutaneously had no change in his circulating eosinophil count at the conclusion of a continuous twenty-four hour intravenous infusion of 2,400 cc. of isotonic sodium chloride solution containing 5.0 mg. of epinephrine.

In 4 patients with rheumatoid arthritis there was no significant change in the circulating eosinophil count four hours after the subcutaneous injection of 0.5 mg. of arterenol (nor-epinephrine). In three other patients the intramuscular injection of 150 mg. of pregnenolone acetate in oil caused no noteworthy change in the eosinophil count. One patient failed to show eosinopenia up to twenty-four hours after the intramuscular injection of testosterone propionate in oil.

EPINEPHRINE THERAPY OF RHEUMATOID ARTHRITIS

Twelve patients with rheumatoid arthritis were treated with epinephrine, 0.5 mg. in saline solution given subcutaneously every six hours for seven to sixty-five days. Table 4 summarizes the observations on these patients. Only 1 patient (M) showed subjective and objective improvement while receiving this therapy. This patient had Reiter's syndrome associated with rheumatoid spondylitis, and the improvement occurred only in the peripheral joints. This improvement was maintained after the treatment was discontinued. Spontaneous remission is common in Reiter's syndrome. This patient's failure to relapse after treatment was discontinued suggests that the improvement was not related to epinephrine therapy. It should be recalled that patients with rheumatoid arthritis treated with either cortisone or pituitary adrenocorticotropic hormone almost always relapse promptly when therapy is discontinued. Two patients were subjectively worse but objectively unchanged while receiving epinephrine therapy, but 3 patients were objectively as well as subjectively worse at the conclusion of treatment. Acute joint flare-ups occurred in 3 patients while they were being treated. The condition in one of these 3 (O) was unchanged at the end of therapy; another (K) experienced variable slight subjective improvement during epinephrine therapy. However, this improvement was not attended by any measurable change in physical observations or sedimentation rate, and he continued to have frequent acute flare-ups during the sixty-five days of treatment.

Because the therapeutic response to pituitary adrenocorticotropic hormone appears to be related to the eosinopenia induced by testing with the drug,[6] it was of interest to determine whether there was any relationship between the therapeutic response to epinephrine and the eosinopenia obtained by this agent. Half of the hospital patients treated showed an inconsistent eosinophil response (M, N, O and Q, tables 3 and 4) to epinephrine testing prior to the institution of therapy; 3 had a consistently significant eosinopenia (C, D and F, tables 3 and 4), and 1 had a consistently insignificant response (F, tables 3 and 4). The therapeutic results in all patients were uniformly disappointing. One of the patients (F), who showed a consistent eosinopenia with as much as a 70 per cent fall in eosinophils during the epinephrine test, experienced while receiving the treatment an acute exacerbation of symptoms in his shoulders, elbows, wrists and hands—joints which had been previously uninvolved.

The fasting eosinophil counts in patients receiving epinephrine showed no consistent difference from those obtained before epinephrine therapy was instituted. Such counts were done five to six hours after therapeutic injections of epinephrine. In 3 of the 8 hospitalized patients the morning counts were slightly lower during therapy than prior to therapy. The patient (O, table 4) in whom this was most pronounced showed an average count during therapy approximately 30 per cent lower than his average count before epinephrine was given. During treatment 5 patients showed a tendency to become refractory to epinephrine in their eosinophil responses four hours after receiving 0.5 mg. of this drug.

Most patients complained of tremulousness, palpitations and headache after the injections of epinephrine.

TABLE 3.—*Nature of the Response of the Circulating Eosinophils to Epinephrine in 16 Patients with Rheumatoid Arthritis Who Had Two or More Tests*

Consistently Significant* Responses		Consistently Insignificant* Responses		Inconsistent Responses	
Patient	No. of Tests	Patient	No. of Tests	Patient	No. of Tests
A	5	H	3	L	4
B	3	J	4	M	3
C	3	K	3	N	7
D	5			O	6
E	4			P	7
F	3			Q	2
G	2				

* A fall of 40 per cent or more was considered significant.

PREGNENOLONE THERAPY IN RHEUMATOID ARTHRITIS

Nineteen patients were given intramuscular injections of pregnenolone or pregnenolone acetate [18] in courses of seven to fifty-one days. Table 5 summarizes the treatment and results in these patients. The dose varied from 100 mg. to 300 mg. Injections were given daily in the majority of cases, but a few patients received injections only two or three times a week. Total dosage ranged from 1,600 to 10,600 mg. With one

18. Dr. Arthur Wright of the Schering Corporation supplied the pregnenolone and testosterone propionate (oreton®) used in this study.

exception (D, table 5) there was no consistent subjective or objective improvement in any of the patients treated. An abstract of the clinical record of patient D, who appeared to respond, is given in table 2. This tation rate remained elevated. There was a three day flare-up of symptoms in the right shoulder from the ninth to the twelfth day of treatment and a subsequent exacerbation of symptoms in his back and shoulders

TABLE 4.—*Treatment of Rheumatoid Arthritis with Epinephrine*

Case	Age	Sex	Type	Duration of Disease	Daily Dose, Mg.	Period of Treatment	Total Dose, Mg.	Results
C	32	M	Mixed*	31 yr.	2.0	14 days	28	Subjectively worse, objectively unchanged
D	29	M	Rheumatoid spondylitis	4 yr.	2.0	20 days	40	Subjectively and objectively unchanged
F	47	M	Mixed	10 mo.	2.0	9 days	18	Subjectively and objectively worse; refused further therapy
K	40	M	Mixed	23 yr.	2.0	65 days	130	Subjectively variable: slightly improved, objectively unchanged
M	39	M	Mixed	5 yr.	2.0	22 days	44	Subjectively and objectively improved
N	36	M	Mixed	6 yr.	2.0	7 days	14	Subjectively worse, objectively unchanged; refused further therapy
O	32	M	Peripheral arthritis	2 yr.	2.0	35 days	70	Acute flare-up during therapy; subjectively and objectively unchanged at close of treatment
Q	50	M	Peripheral arthritis	10 mo.	2.0	29 days	58	Subjectively and objectively worse; bilateral knee effusion developed during treatment
Si	52	M	Peripheral arthritis	12 yr.	2.0	14 days	28	Patient requested that treatment be discontinued
Sch	51	F	Peripheral arthritis	6 yr.	2.0	28 days	56	Subjectively and objectively worse
Br	72	F	Peripheral arthritis	18 yr.	2.0	14 days	28	Unchanged
Bo	45	F	Peripheral arthritis	10 yr.	2.0	14 days	28	Unchanged

* Coexistent peripheral arthritis and spondylitis.

TABLE 5.—*Treatment of Rheumatoid Arthritis with Pregnenolone*

Case	Age	Sex	Type	Duration of Disease, Yr.	Daily Dose, Mg.	Duration of Therapy, Days	Total Dose, Mg.	Sedimentation Rate* Before	Sedimentation Rate* After	Results
B	45	M	Rheumatoid spondylitis	6	300	15½	4,650	15	20	Subjectively worse, objectively same; refused further therapy
D	29	M	Rheumatoid spondylitis	4	300	27	6,600	19	19	Improvement in motion of spine
G	42	M	Peripheral arthritis	3	300	8	2,400	28	26	No change
H	29	M	Rheumatoid spondylitis	8	100	16	.....	..	..	No change
					300	7	3,700	21	18	No change
J	39	M	Rheumatoid spondylitis	7	100	22	.....	..	..	No change
					300	28	10,000	24	25	No change
K	40	M	Mixed †	23	100	16	1,600	24	25	No change
L	34	M	Rheumatoid spondylitis	5	300	14	4,200	14	19	Subjectively worse, objectively unchanged; refused further therapy
N	36	M	Mixed †	6	300	7	2,100	22	20	No change
R	35	M	Mixed †	12	300	14	.....	..	..	Joint flare-up on medication
						6	6,000	8	15	
P	26	M	Rheumatoid spondylitis	5	300	13	3,900	8	19	Subjectively worse, objectively unchanged; refused further therapy
Ga	39	F	Peripheral arthritis	..	100	14	1,400	17	15	No change
Lu	65	M	Peripheral arthritis	..	100	14	.....	85	65	No change
					P‡ 50 plus T§ 50	10	P 1,000 plus T 500	65	65	No change
Gy	50	F	Peripheral arthritis	..	100	10	1,000	53	100	Worse
Ru	36	M	Rheumatoid spondylitis	..	100	29				
					P‡ 50 plus T§ 50 three times a wk.	12	P 6,400 plus T 300	62	54	Marked subjective improvement, then relapse; no objective change
					200	16				
Sch	51	F	Peripheral arthritis	..	100	28	2,800	72	50	No change
Py	17	F	Peripheral arthritis	..	100	5	500	52	51	No change
Co	20	M	Peripheral arthritis	2	200	14	2,800	..	..	No change
Br	72	F	Peripheral arthritis	18	200 twice a wk.	6	1,200	62	54	No change
Pl	41	M	Rheumatoid spondylitis	5	200	11	2,200	24	21	No change

* By Cutler method in the first 10 patients in the table and by Westergren method in the remainder.
† Coexistent peripheral arthritis and spondylitis. ‡ P indicates pregnenolone. § T indicates testosterone.

patient had a fluctuating course, but some joints showed gradual improvement in mobility beginning four days after the institution of treatment. It should be noted, however, that tenderness of the dorsal portion of the spine, muscle spasm and moderately severe, intermittent night pain and morning stiffness were still present at the conclusion of therapy. His sedimen- during the third week of therapy. His general condition was somewhat improved, and this improvement bore at least a time relationship to treatment with pregnenolone acetate. After cessation of therapy he continued to show further improvement in forward flexion of the spine, although there subsequently developed a recurrence of pain in the hips. A second

patient (Ru, table 5) with rheumatoid spondylitis reported fairly extensive subjective improvement at the end of the first week of therapy. This was not attended by objective evidence of benefit, and after one month of continuous therapy the patient gradually relapsed to the symptomatic state that existed prior to institution of pregnenolone treatment.

Most patients complained of moderate to severe pain at the site of injection, but there were no untoward reactions.

TESTOSTERONE PROPIONATE IN THE TREATMENT OF RHEUMATOID ARTHRITIS

Thirteen patients were treated with testosterone propionate in oil. Of these, 11 had rheumatoid arthritis and 2 had chronic tophaceous gouty arthritis. Table 6 summarizes the observations in these cases. Two patients with rheumatoid arthritis were treated with a combination of pregnenolone acetate and testosterone. The dosage of testosterone was 100 to 200 mg. injected intramuscularly either daily or two or three times a week. The total dosage ranged from 500 to 1,800 mg. In no instance was there a true remission of the disease. In 3 patients moderate improvement was noted, but this improvement was entirely subjective. In the two patients with chronic tophaceous gouty arthritis there was definite worsening of the symptoms after early amelioration. Several patients experienced malaise as well as an increase in their rheumatoid symptoms. We were unimpressed with any tonic effect. In 2 instances there was definite evidence of water retention manifested by dependent edema and weight gain. Other untoward reactions noted were a deepening of the voice and increased hair growth on the upper lip in 2 women. None of the male patients admitted having any change in libido.

TABLE 6.—*Treatment of Rheumatoid Arthritis and Gouty Arthritis with Testosterone Propionate*

Case	Age	Sex	Type	Duration of Disease	Daily Dose, Mg.	Duration of Therapy, Days	Total Dose, Mg.	Sedimentation Rate*		Results
								Before	After	
M	45	F	Peripheral arthritis	10 yr.	100	6	.....	..	..	.....
					200	6	1,800	92	84	No improvement
Ga	39	F	Peripheral arthritis	7 yr.	100	5	500	15	24	No improvement
Gy	50	F	Peripheral arthritis	9 yr.	100	5	500	100	86	Worse
Lu	65	M	Peripheral arthritis	9 yr.	100	8	800	85	72	Minor improvement
Si	52	M	Peripheral arthritis	8 yr.	100	14	1,400	42	26	Minor improvement (subjective)
Py	17	F	Peripheral arthritis	6 mo.	100	8	800	52	38	No improvement
In	47	F	Peripheral arthritis	9 yr.	100	6	600	13	18	Minor improvement (subjective)
By	53	F	Peripheral arthritis	26 yr.	100	6	600	95	55	Worse
Sch	46	F	Peripheral arthritis	6 yr.	100	5	500	50	75	Worse
He	36	F	Peripheral arthritis	6 yr.	100 twice a week	10	1,000	46	33	Worse
Br	72	F	Peripheral arthritis	18 yr.	100 three times a week	8	800	83	87	Worse
								Uric Acid (Mg./100 Cc.)		
Di	43	M	Gouty arthritis	11 yr.	100	10	1,000	7.0	7.4	Improvement, then worse
Ep	54	M	Gouty arthritis	11 yr.	100	10	1,000	7.2	8.6	Improvement first day, then worse

* Westergren method.

COMMENT

The natural course of rheumatoid arthritis is such that evaluation of treatment is exceedingly difficult. Improvement, when it occurs spontaneously, is usually a gradual phenomenon. The prompt and dramatic remission almost universally effected by cortisone and pituitary adrenocorticotropic hormone provides a standard by which various forms of hormonal therapy may be measured. The improvement brought about by gold salts and other therapeutic agents takes a much longer time, but nothing has been reported to suggest that the pharmacologic behavior of the agents used in this study is in any way similar to that of gold salts. In some of the published reports the inference has been that the action of these agents (epinephrine, pregnenolone and testosterone) is similar to that of the endocrine substances, cortisone and pituitary adrenocorticotropic hormone, proved to be effective in this disease. Because of the course of rheumatoid arthritis and the new standard of measurement which has recently been provided, one is justified in being somewhat skeptical of hormonal agents which must be administered for long periods of time in order to bring about improvement. Furthermore, reports of "slight," "grade 1" or even "moderate" improvement in rheumatoid arthritis are of doubtful significance in view of the nature of the disease. Frequently repeated and painstakingly performed examinations must be made in order to ascertain the value of therapeutic agents in this disease. Objective improvement must be demonstrated to parallel subjective improvement in order to credit an agent as being effective.

In the present study the number of patients treated with these three agents is small and the periods of observation have been short. It may be that larger amounts of the drugs given over a longer period of time, or with a different schedule of doses, would have a more beneficial effect. There is a reasonably plausible rationale for the use of epinephrine in rheumatoid arthritis. The rationale for the use of testosterone, pregnenolone and estrogenic hormones either alone or in various combinations is less clear, and in this investigation pregnenolone and testosterone have been found to be as consistently disappointing in the treatment of rheumatoid arthritis as was epinephrine. The negative results and some of the unpleasant side effects have led us to believe that these agents offer no real promise in the treatment of rheumatoid arthritis.

CONCLUSIONS

1. Some patients with rheumatoid arthritis fail to manifest significant eosinopenia after the subcutaneous administration of 0.5 mg. of epinephrine. Furthermore, after repeated testing the response may be inconsistent and unpredictable on the basis of previous performances.

2. The subcutaneous administration for seven to sixty-five days of 0.5 mg. of epinephrine four times a day to 12 patients with rheumatoid arthritis failed to influence the course of the disease.

3. There was no relationship between the eosinopenia produced by epinephrine and the therapeutic response to treatment with epinephrine.

4. Intramuscular injections of pregnenolone or pregnenolone acetate daily or two or three times a week resulted in no improvement in 17 cases of rheumatoid arthritis. One patient with rheumatoid spondylitis improved objectively and subjectively. In 1 patient with rheumatoid spondylitis there was minor subjective improvement at the end of one week's treatment, but this was followed by gradual relapse in the face of continued therapy.

5. Intramuscular injections of testosterone propionate, 100 to 200 mg. daily or two or three times a week, in 11 patients with rheumatoid arthritis and in 2 patients with chronic tophaceous gouty arthritis failed to result in any consistent improvement.

33 East Sixty-First Street (21).

SURGICAL TREATMENT OF BRONCHIECTASIS IN CHILDREN

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Since adequate reports of pulmonary resection in children are lacking, it is felt timely to present the results of surgical treatment in 25 cases of bronchiectasis in children. One of the common causes of cough is bronchiectasis. Laennec, many years ago, stated that for every 4 cases of bronchiectasis in the adult, 3 had their origin in childhood. In view of the morbidity and mortality accompanying this lesion, it is of the utmost importance that early recognition and adequate therapy be carried out. The only successful treatment to date is surgical extirpation of the suppurative lung disease.

It is estimated that bronchiectasis represents about 5 per cent of all diseases in childhood. The classic symptoms are cough, sputum and hemoptysis. The patients are subject to numerous infections of the upper respiratory tract and recurrent attacks of pneumonia. The principal complications are direct extension of the infection, pneumonia, empyema, pulmonary abscess formation, metastatic abscess (especially brain abscess) formation and hemorrhage. The disease is chronic and progressive, and the course is downhill unless the condition is adequately treated.

There are many theories concerning the pathogenesis of bronchiectasis. Mallory [1] stated that the usual case is caused by primary bronchitis and secondary atelectasis. Therefore, the best line of attack appears to be prevention or prompt alleviation of atelectasis. The morbidity and mortality rates convince one that treatment is definitely needed. Perry and King,[2] on the basis of follow-up examination of 400 patients, concluded that in twelve years the mortality of the patients who had not undergone surgical intervention was 26 per cent, 41 per cent of the patients dying within five years of onset. In the fatal cases 70 per cent of the patients died directly of the disease. There is evidence that patients in whom bronchiectasis develops before the age of 10 do not live beyond the age of 40.[3]

In consequence, it is generally agreed that the definitive treatment of bronchiectasis is surgical. Although medical management may appear to alleviate the symptoms, it is only palliative, and the mortality and morbidity rates remain elevated. The treatment of choice is early pulmonary resection, provided not too great a portion of lung tissue must be sacrificed. Riggins [4] states that the physician who routinely advises young adults with operable bronchiectasis against surgical procedures is assuming a great responsibility and, in all probability, renders his patient a great disservice.

RESULTS OF SURGICAL INTERVENTION

There have been no detailed reports concerning the surgical treatment of bronchiectasis in children. This report is based on the personal surgical treatment of 25 children with bronchiectasis. There were twenty-eight separate operations for pulmonary resection.

Bronchoscopic examinations of all children were done before surgical intervention for the detection of any possible foreign bodies, and an evaluation of the tracheobronchial tree with regard to bronchitis, erosion or obstruction was made. Complete bronchographic examinations with iodized oil were made of all children to establish a definite diagnosis of bronchiectasis and to determine the exact location and extent of the suppurative process, which is mandatory in determining the amount of the lung tissue to be resected. If all involved areas cannot be resected, because of the extensive nature of the process, at least something definite is available on which a prognosis may be based.

All operations were performed with the protection of sulfonamide drugs, penicillin and, in several of the recent cases, streptomycin. A vigorous program of preoperative preparation was used, consisting of oral administration of sulfonamide drugs, intramuscular and aerosol administration of penicillin, postural drainage when the sputum was profuse and frequent bronchoscopic aspirations. At operation, penicillin and streptomycin were instilled into the pleural cavity before the chest was closed. Penicillin and streptomycin therapy was continued postoperatively for a period of four or five days. The surgical technic consisted of individual ligation of all hilar vessels and closure of the bronchus with individual silk sutures; the bronchus was then covered with pleura. Bronchoscopic examinations of all patients were made at the conclusion of the operations. Frequent postoperative bronchoscopic examinations and tracheal aspirations were used to prevent bronchial obstruction and failure of expansion. Routine closed drainage was used in all cases on closure of the chest. Prompt thoracentesis was done in the presence of effusion.

The ages of the children varied from 2 to 12, with an average of 7 years. All gave a definite history of chronic cough and pneumonia; several had previously had attacks of hemoptysis. In most instances the onset of trouble started with measles, pertussis or pneumonia; in 2 cases, however, the onset was related to the aspiration of a foreign body, after attempts to remove it bronchoscopically had failed. One child had splenomegaly of undetermined origin (Banti's syndrome) and had previously undergone splenectomy. There was 1 patient with the triad of Kartagener—situs inversus, pansinusitis and bronchiectasis. All were demonstrated to have bronchiectasis by bronchographic examination with iodized oil. Six of the patients had bilateral involvement. In addition, 1 patient with

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1. Mallory, T. E.: Pathogenesis of Bronchiectasis, New England J. Med. **237**: 795, 1947.
2. Perry, K. M. A., and King, D. S.: Bronchiectasis: Study of Prognosis Based on Follow-Up of Four Hundred Patients, Am. Rev. Tuberc. **41**: 531, 1940.
3. Strieder, J. W.: Surgical Aspects of Bronchiectasis, New England J. Med. **238**: 109, 1948.
4. Riggins, H. N.: Cited by Strieder, J. W.[3]

extensive bronchiectasis throughout one lung had chronic empyema with a bronchopleurocutaneous fistula. There were 21 patients subjected to unilateral lobectomy or segmental resection; 2 had pneumonectomy, and 2 had bilateral pulmonary resection (table 1).

It is important to note that the process was almost exclusively localized in the lower lobes, the middle lobe of the right lung or the lingular segment of the upper lobe of the left lung. In complete preoperative bronchographic examination, bronchiectasis was demonstrated in an upper lobe only three times: in 1 case the lesion was minimal and was not resected; the other 2 patients were children in whom the entire left lung was extensively involved and pneumonectomy had to be carried out.

There had been no mortality to the time of writing. The complications consisted of empyema in 1 patient (treated successfully with rib resection and drainage); serious infection of the wall of the chest which finally healed after a rather prolonged period in 1 patient; minor wound infection in 1 patient, and laryngeal edema, which developed postoperatively in a 7 year old girl on whom tracheotomy was performed in order to relieve the obstruction (table 2).

In 16 cases the results were excellent. These children, at the time of writing, were completely free of all symptoms (table 3). It is significant that in these children all the diseased lung tissue could be resected. All had unilateral involvement preoperatively; however, pneumonectomy was necessary in 2 cases.

In 7 cases the results are classified as good. These children, while free of symptoms, are still subject to rather frequent attacks of infection of the upper respiratory tract which are successfully controlled by a few days of bed rest and antibiotic therapy. Among these 7 with good results are 4 cases in which there originally was bilateral involvement.

The result in one patient in particular may be mentioned. A 7 year old girl was subjected to three separate operations for bilateral pulmonary resection over a period of two years. The preoperative diagnosis was bronchiectasis of the lower lobes of both lungs and minimal involvement of the lingular segment of the upper lobe of the left lung. At the first operation the lower lobe of the left lung was removed, and this was followed by removal of the lower lobe of the right lung about one year later. The child was greatly improved, but some symptoms persisted, and, finally, at the third operation, the lingular segment was removed. This child has now been followed for five years and the results are considered good. The other 3 cases of bilateral involvement in this group were not considered severe enough to warrant bilateral resection. The removal of the more extensive areas has produced good results, but it is realized that these patients need careful observation and that they may eventually need additional surgical treatment.

Two patients with bilateral involvement were definitely improved by surgical intervention. One underwent bilateral lobectomy. These children, unfortunately, still have cough and sputum production. Originally, these 2 children had rather extensive bilateral disease. How their health will be affected over a period of time remains to be seen; however, surgical procedures have offered palliation and have definitely improved their general condition.

Examination of the resected lung tissue revealed definite bronchiectasis in all the specimens. In addition to bronchiectasis, there were atelectasis, pneumonitis and small pulmonary abscesses. These findings are important, as they definitely confirmed the preoperative diagnoses made by bronchographic examination.

In reviewing these results one is greatly impressed with the necessity of early recognition and prompt treatment in order to obtain the best results.

COMMENT

This report is based on the results in 25 consecutive cases of bronchiectasis in children treated by pulmonary resection. The follow-up studies range from six months to five years. While the follow-up period is short, an impression at least, can be formed.

Morbidity and mortality figures convince one that definitive treatment is needed for children with bronchiectasis. The diagnosis of bronchiectasis is simple and accurate. The only type of therapy which is definite and successful is surgical extirpation of the suppurative process. Children tolerate pulmonary resection exceedingly well. With present technics and antibiotic therapy, the dangers of surgical procedures are minimal. The results of surgical intervention, in the relief of symptoms, are inversely proportionate to the extent of the involvement, and, obviously, the less lung tissue involved, the less lung tissue which need be sacrificed.

This is a plea for the early diagnosis and definitive treatment of bronchiectasis to be carried out in childhood. Early treatment will obviate the hazards of bronchiectasis which must be faced if the patient grows to adult life without surgical removal of the diseased area. Realtively extensive bilateral pulmonary resection can be carried out without causing the patient any kind of respiratory embarrassment.

TABLE 1.—*Lung Tissue Resected in Twenty-Eight Operations*

Area Resected	No.
Entire left lung	2
Lower lobe of left lung	16
Lingular segment of upper lobe of left lung	5
Lower lobe of right lung	9
Middle lobe of right lung	4

TABLE 2.—*Complications in Twenty-Eight Operations*

Complications	No.	Percentage
1. Mortality	0	0
2. Morbidity		
a. Empyema	1	3.56
b. Infection of the chest wall	1	3.56
c. Infection of the wound	1	3.56
d. Laryngeal edema (tracheotomy)	1	3.56

TABLE 3.—*Results of Surgical Intervention on 25 Children*

Results	No. of Cases	Percentage
Excellent (cured)	16	64
Good (no symptoms)	7	28
Improved	2	8

SUMMARY

1. The problem of bronchiectasis is briefly reviewed. It is pointed out that the definitive treatment is surgical removal of the suppurative process and that the best results are obtained when this removal is carried out early.

2. The diagnosis of bronchiectasis is made only by means of roentgen examination with the injection of a contrast medium, such as iodized oil, into the bronchi. All five lobes should be adequately filled.

3. The results in 25 consecutive cases of bronchiectasis in children treated surgically are presented.

4. The safety of the procedure cannot be overemphasized.

DELAY IN DIAGNOSIS AND TREATMENT OF CANCER

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JOHN E. LEACH, M.D.
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From the standpoint of cancer control, the public and medical profession have not advanced at the same rate as has knowledge of the clinical aspects of the disease. This problem is of greater magnitude each successive year because the population is aging, i. e., an increasingly larger segment of the population is surviving to reach the period of life when cancer is more frequent. The net result is a larger mortality and morbidity from cancer each year—estimated at 300,000 for 1949.

While physicians search for an adequate screening test to detect cancer or hope for a panacea, they are still faced with the current problem of attempting to reduce the number of deaths due to cancer. Today, despite considerable progress in diagnosis and therapy, the only practical means of reducing the over-all mortality and morbidity from cancer is early detection of lesions and the prompt application of adequate therapy. Although it is true that newer methods or improved procedures in radiation and surgery yield larger cure rates, in the main such salvage is made up of patients with localized or relatively localized disease. It is seldom possible to reclaim the patient with advanced cancer.

In 1946 we made a comparative study of the causes for delay in the diagnosis of cancer.[1] The results were disappointing, and the physician was shown at a disadvantage. A similar survey was made in 1947 and in 1948. This report is a summary of the data in these latter two years and a comparison with the previous data of 1923-1938[2] and of 1946. It is our opinion that consecutive annual studies give some indication of the trends in diagnostic delay and incidentally some evidence of the effect that the cancer educational program (lay and professional) has had in this particular metropolitan area (New York).

METHOD OF STUDY

The study of 1947 was made in the same manner as that of 1946, using a random sample of 500 patients with cancer examined from Jan. 1 to April 1, 1947. The study of 1948 ran from July 1 to December 31 and consisted of all patients (839) examined in the admitting clinic, in whom a diagnosis of cancer was proved at Memorial Hospital. No other method of selection was used. During the period covered in the 1947 study there was increased publicity concerning cancer, culminating in "cancer month." There was no such unusual publicity during the period covered in the 1948 study. The data used in both studies were obtained by physicians during the initial admitting examination, and the patients were not aware that a special survey was made. The questions were not unusual and consisted of, "When did you notice your first symptoms? When did you first consult a physician?" and the like. The ground rules set by Pack and Gallo in their 1923-1938 survey[2] were used to determine culpability and delay in diagnosis and treatment:

1. The patient was considered at fault: (*a*) if he delayed three months or more after first symptoms before he consulted a physician, or (*b*) if he refused to follow acceptable advice such as biopsy, roentgen studies or referral to a suitable person, hospital or clinic.

2. The physician was considered culpable: (*a*) if he failed to arrive at a diagnosis in a month or, when unable to do so, did not refer the patient to a suitable person, hospital or clinic; (*b*) if he failed to give proper advice or counsel at all or to apply proper therapeutic measures, or (*c*) if he failed to refer the patient to a suitable person, hospital or clinic when the patient failed to improve.

3. Naturally, when a combination of the aforementioned factors was present, the physician and the patient were considered jointly responsible for the delay.

Again it must be emphasized that the data obtained are solely from patients, are biased in their favor and do not necessarily portray the true situation in the area served by Memorial Hospital, much less in the county at large. However, data similarly biased are valid when used for comparison.

RESULTS

The data were first studied from the over-all point of view (fig. 1). The 1948 results are encouraging in that they show improvement over those for 1947; they are discouraging in that they are essentially the same as those in 1946. One favorable sign is a trend toward improvement, i. e., a decrease of culpability, in physicians. It is slight but at least in the desired direction. The patient has improved over 1947 but only to the point where he was two years earlier in 1946.

We are still of the opinion that many patients with cancer who had previously consulted a physician had not received an adequate physical examination. To evaluate this factor in culpability and in delay in diagnosis of cancer patients were put in four groups.

1. The superficial group consisted of those with cancers that could be detected or suspected by a superficial examination. Examples are cancer of the skin, lip and anterior part of the tongue. One third of the group had cancer of the skin.

2. Those with cancers of the breast were placed in a separate category chiefly because of the publicity given to this form of cancer in the past.

3. The thorough group consisted of those with cancers that could be detected or suspected by a careful history and complete physical examination. Examples are cancer of the floor of the mouth; of the posterior two thirds of the tongue; gynecologic cancer; cancer of the distal part of the rectum and anus, and malignant lymphoma.

4. The special group consisted of those with cancers that could be detected or suspected by a careful history and complete physical examination plus roentgenographic or endoscopic studies, or both. Examples are cancer of the lung, esophagus, stomach, upper part of rectum and colon and cancer of the kidney and bladder.

Superficial Group.—The comparative data for the superficial group are shown in figure 2. It is evident that there was an improvement in all categories from 1947 to 1948, but there was no gain over 1946. It is amazing how closely the 1946 results approximate those of 1948.

Breast Group.—The breast group is the best from the standpoint of no delay. The comparative data are shown in figure 3. There has been an improvement over 1946. To the credit of the members of the medical profession, the greatest improvement has been in the

From the Medical Department and the Department of Statistics, Memorial Hospital.

1. Leach, J. E., and Robbins, G. F.: Delay in the Diagnosis of Cancer, J.A.M.A. **135**: 5-8 (Sept. 6) 1947.

2. Pack, G. T., and Gallo, J. S.: Culpability for Delay in the Treatment of Cancer, Am. J. Cancer **33**: 443-462 (July) 1938.

physician only category. Conversely, the bulk of this effect is observed in the no delay group.

Thorough Group.—The comparative data for the thorough group are given in figure 4. There has been some improvement in all categories, but it is only of slight degree.

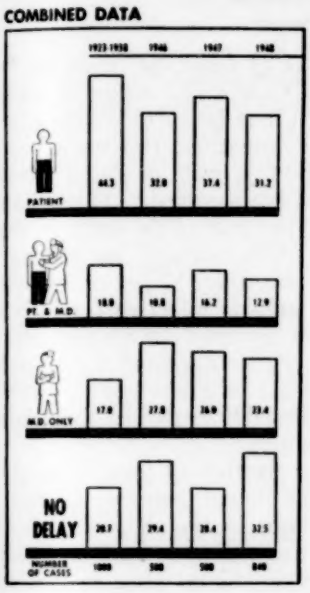

Figure 1

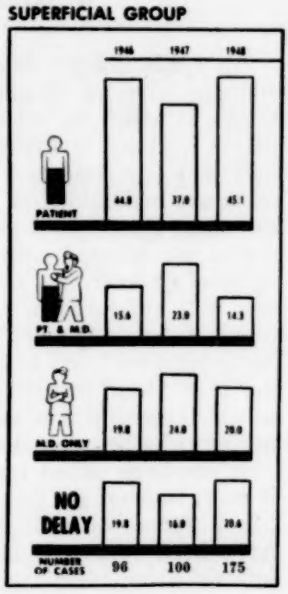

Figure 2

Fig. 1.—Combined data on culpability for delay in diagnosis and treatment of cancer. Figures for 1923-1938 from Pack and Gallo [2] and for 1946 from Leach and Robbins.[1]

Fig. 2.—Culpability for delay in diagnosis and treatment of cancer in superficial group.

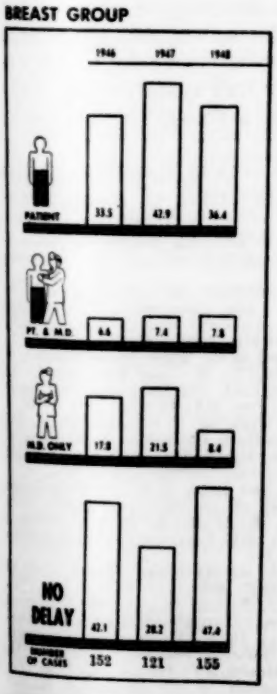

Figure 3

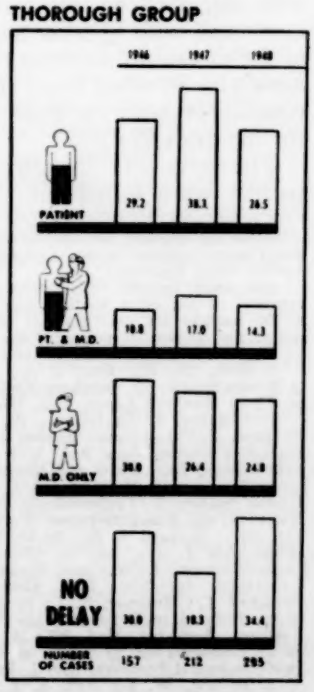

Figure 4

Fig. 3.—Culpability for delay in diagnosis and treatment of cancer in breast group.

Fig. 4.—Culpability for delay in diagnosis and treatment of cancer in thorough group.

Special Group.—The data for the special group are compared in figure 5. The patient of 1948 has improved over 1947 but not quite to the level of 1946. The physicians only category has shown the most heartening improvement over 1946 but curiously not much improvement over 1947. The improvement in the no delay group is due almost solely to the better showing of the physicians. This is particularly encouraging because this group includes lesions with high early mortality and with which the bulk of cancer mortality rests.

LAPSE OF TIME

The data were again analyzed from the standpoint of the lapse of time between the onset of first symptoms to the first consultation with a physician and from that temporal point until a diagnosis was made and treatment started. Median times in months were used.

The comparative data (fig. 6) reveal the encouraging trends observed. There has been a consistent improvement in all groups in 1948. At least 50 per cent of the sample of patients wait a shorter time from the onset of symptoms before a physician is consulted. Moreover, the patient and the physician lose less time in arriving at a diagnosis and beginning therapy. One discouraging observation is the length of time it takes for the physician and the patient to arrive at a diagnosis and to

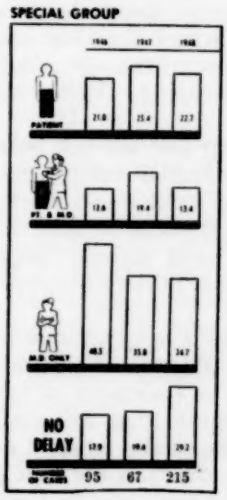

Figure 5

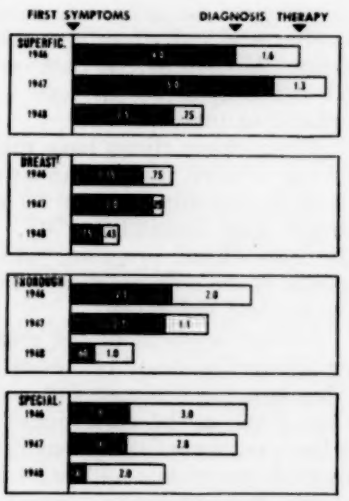

Figure 6

Fig. 5.—Culpability for delay in diagnosis and treatment of cancer in special group.

Fig. 6.—Comparison of time lapse (median in months) for the superficial, breast, thorough and special groups in 1946, 1947 and 1948 from detection of first symptoms to verification of diagnosis and institution of treatment.

start treatment in the special group. Of all the groups, this is one in which speed in diagnosis and rapid institution of therapy are of the utmost importance.

COMMENT

On cursory review, these data are not as encouraging as might have been hoped, considering the tremendous efforts that have been spent in education. However, there are certain distinct signs of improvement. The physicians have lessened delay in diagnosis significantly since 1946 except in lesions of the superficial group. There has been a sizeable gain in rapid diagnosis and treatment for patients in the breast, thorough and special groups. The reduction of delay in the breast group is of the greatest magnitude (more than 50 per cent). In the special group in which diagnoses are certainly more difficult and time consuming, requiring greater cooperation on the part of the patient and the physician, the improvement is no less encouraging. This is the group in which the mortality is extremely high and in which such gains mean saved lives.

Another encouraging aspect of these data is the decided decrease in the time both from the onset of first

symptoms to first consultation and from first consultation to diagnosis and the start of therapy. This also results in increased survival rates.

The slow decrease in delay on the part of the patient is discouraging. The reasons for patient delay are not always easy to determine. In a parallel study by the Social Service Department of this hospital on diagnostic delay in the patient with cancer, one factor stood out. The clinic patient, and this probably applies to the average patient, handles an illness due to cancer much the same as he has handled similar life situations in the past. The patient who is accustomed to face reality or who fears physical pain or disability and who is accustomed to seek medical aid promptly also seeks help quickly when his illness is due to cancer. Conversely, the patient who in the past had to be forced by circumstance, intractable pain or the pressure of family or friends to seek medical aid acts the same way when his illness is due to cancer. One might state that in a given patient the reaction pattern is set long before the cancer develops. Economic status seemed to be of no consequence in the group of patients studied so far as delay or nondelay was concerned. Better levels of intelligence and education were factors favoring nondelay. Unfortunately, data on those in the age groups 60 and over were the least encouraging. Delay was greater in these patients.

These observations have meaning and are not based on one isolated study. Similar conclusions were reached in an independent survey by a different social worker in the same hospital in 1947. They mean in part that the educational program, which must include propaganda, is the only practical weapon at present to combat inertia and ignorance.

A large segment of the population is never reached or affected by many phases of the educational program. This is not a criticism but simply a statement of fact. One phase of the educational program that will reach a large portion of the population, especially those in the desired age groups (40 years and older) is the type of steady enlightening propaganda that the individual physician can spread. Not the least important measure is the routine annual physical examination. This is too great a task to impose on the cancer detection clinic. Each physician has his own detection clinic in his office and hospital. Let them be used!

This study, in contrast to that of 1946, indicates that the physician is improving in his handling of patients in the breast, thorough and special groups, although he has not lessened delay in detecting lesions of the superficial group. Moreover, the total delay period (time lapse) has been shortened. Both these improvements mean increased human salvage.

CONCLUSIONS

1. A comparative study of delay in the diagnosis of cancer covering four periods (1923-1938, 1946, 1947 and 1948) shows improvement over 1923-1938 but no gains since 1946.

2. Despite the lack of gross improvement, patients are losing less time between the onset of first symptoms and the first consultation with a physician.

3. The gross reduction in delay since 1946 has been due to an improvement on the part of the physician.

4. In addition, physicians are losing less time between the time of first consultation and the time the diagnosis is established and therapy is applied.

5. Certain aspects of the cancer control problem in the light of these data have been discussed.

Q FEVER: TRANSMISSION FROM ONE HUMAN BEING TO OTHERS

Report of Three Cases

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An epidemiologic study of Q fever, as made in the endemic area of southern California, suggests three modes in which the infection may be spread: (*a*) occupation in dairy or livestock industries, (*b*) use of raw milk and (*c*) residence within ¼ mile of places where cattle are maintained or beef is processed.[1] It has been estimated that more than 10 per cent of the cattle in this region are infected with Coxiella burnetii, the etiologic agent of Q fever, and that more than 50 per cent of the raw milk produced in this area is infective for guinea pigs.[2] Cases of Q fever have occurred among slaughterhouse workers [3] and laboratory technicians.[4] C. burnetii has been found in ticks,[5] and 1 case has been reported in which the infection was probably caused by the crushing of ticks between the fingers.[6]

It has been stated repeatedly that Q fever is rarely, if ever, transmitted from one human being to another.[7] Six instances of multiple cases in the same household have been reported, but the patients were probably infected from identical sources rather than by human contact.[1] Three clinical and 3 subclinical cases have been reported which resulted from the handling of contaminated material.[8] Several autopsy attendants apparently acquired an infection through contacts with Q fever victims.[9]

That human to human transmission of Q fever exists was suggested by our recent observation of a patient acutely ill with Q fever and the subsequent appearance of the disease in fourteen to twenty-three days in 3 persons who attended him. They had symptoms clinically compatible with Q fever and serologic tests positive for the disease.

The serums of 26 other persons in contact with this patient were tested for the presence of complement-

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Drs. M. Mieras and M. Weiss assisted in the ward care of patients.

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9. Huebner, R. J.: Personal communication to the authors.

fixing antibodies to C. burnetii antigen. Of these, 2 had positive tests (1:64 titer) but were asymptomatic. The titer of 1 dropped to 1:32 two months later. The other was not available for follow-up. It cannot be stated that these antibody responses resulted from a previous exposure to Q fever or from a subclinical infection resulting from this exposure.

Another contact, who was also a roommate of a patient (case 3) with the disease, became ill two days after the latter with symptoms suggestive of Q fever. These included sweats, shaking chills, fever, retrobulbar headache and anterior chest pain bilaterally. These symptoms subsided in four days. The serologic test for Q fever performed one month later was negative. This may represent a case of Q fever without production of a perceptible antibody response.

None of the personnel resided near a dairy, had contact with livestock or ingested raw milk; however, they did handle bed linen, clothes, bed pans and food trays of the patient (case 1) and had personal contact with him. No conclusions could be made as to the possible mode of transmission in these cases.

REPORT OF CASES

CASE 1.—C. W. (the patient who is presumed to have infected the nurse and attendants) was a man 55 years of age, an unemployed mechanic and salesman, who lived more than 2 miles from a dairy or stockyards and had not been outside the immediate vicinity of his home for several months prior to this illness. He had had no previous similar illness. For the past two years he had consumed an average of 1 pint (473 cc.) of raw milk daily from the same dairy. He lived with his brother and sister-in-law, who also drank raw milk but who were serologically negative for Q fever.

The onset of his illness occurred on May 1, 1949 with malaise, shaking chills, fever, lassitude and drowsiness. His physician administered penicillin. Four days later the patient manifested delirium, which persisted for nine days. Eight days after onset (May 8) he was admitted to the hospital. He was disoriented, confused and acutely ill. The posterior pharynx was diffusely reddened. The chest was dull to percussion and had decreased tactile fremitus over the left base posteriorly and laterally. The remainder of the physical examination was noncontributory.

A roentgenogram of the chest showed diffuse density of the lower portion of the left lung. Subsequent roentgenograms showed gradual resolution of this process. Unfortunately, a blood specimen was not taken during the acute stage of the illness for the complement fixation test with C. burnetii antigen.[10] Subsequent blood specimens were positive for Q fever in the following dilutions: June 3, 1:8,092; June 17, 1:8,092; August 2, 1:2,048, and September 22, 1:2,048. The June 17 specimen was positive in a 1:4,096 dilution when tested concurrently. On admission the urine contained albumin (4 plus) and many coarse granular casts. This observation disappeared after hydration. The initial blood count was 3,600,000 red blood cells with 70 per cent hemoglobin and 2,400 white blood cells with 60 per cent neurtophils and 32 per cent lymphocytes. Subsequent counts showed a persistent leukopenia and granulocytopenia with 0 to 9 per cent neutrophils. The sedimentation rate was 35 mm. in one hour with the Cutler method. The routine agglutination tests for typhoid, paratyphoid, brucella and Proteus (Weil-Felix) were negative. The cold hemagglutination and heterophil antibody tests were negative. Spinal fluid examination gave normal results. Spinal fluid and blood cultures were sterile. A positive reaction of his blood to the Kahn test, which was observed during the acute stage of his illness, became negative during convalescence. Reaction to the Kolmer modification of the Wassermann test was negative at all times.

At the time of admission it was believed that the patient had a severe case of pneumonia with toxic depression of the granulocytes. He was treated with oxygen, penicillin and sulfadiazine. Since he showed no response to this therapy after two days, he was started on 4.5 Gm. of aureomycin hydrochloride orally and 1 Gm. of streptomycin hydrochloride intramuscularly daily. He was also given multiple blood transfusions. His temperature continued to show a daily rise to 106 F. rectally for six days. Then he began to improve, and six weeks later, when he was asymptomatic, aureomycin therapy was discontinued. He continued to be asymptomatic.

The granulocytopenia, which persisted even after convalescence, was difficult to explain. The patient had taken cinchophen for several months prior to entry and a high potency vitamin D preparation for four years. However, there was no improvement in his blood picture following the withdrawal of the drugs. Several months later the patient was readmitted to the hospital with severe furunculosis. The blood picture was the same. After repeated blood and marrow studies he underwent a splenectomy for presumed hypersplenism. Postoperatively his white blood cell count rose and stabilized at 5,200 cells with 31 per cent neutrophils and 58 per cent lymphocytes.

CASE 2.—L. L., a woman aged 48, was the nurse who attended the first patient (case 1) from the time of his admission. On May 31, twenty-three days after the first patient was admitted, she complained of supraorbital headache, nausea, chills and mild fever. Four days later these symptoms had intensified and, in addition, she had shaking chills and complained of lethargy. The next day she had vertigo, more generalized headache, mild nonproductive cough, dysuria and urinary frequency. Her physician prescribed penicillin and a sulfonamide drug, but there was no improvement. Five days later, or ten days after the onset of her symptoms, she was admitted to the hospital. She was acutely ill. Her temperature was 100 F. orally, and she had a slightly injected pharynx.

The roentgenogram of the chest showed pneumonia in the left upper lobe. The blood was normal except for a mild secondary anemia. Routine agglutination tests were negative. The urine was normal. Reactions of her serum to C. burnetii antigen were as follows: July 1, 1:64; July 20, 1:128, and September 8, 1:64. Two days after admission the patient was afebrile. After twenty-two days the pneumonia showed complete resolution by roentgen observation. This case followed the usual pattern for Q fever, except for lack of a daily rise in temperature.

CASE 3.—A. McI., a white man aged 33, was an attendant of the first patient (case 1) from the time of his admission. Two weeks later (May 22) he noted decided tiredness and malaise. The next day he had shaking chills, fever (103 F. orally), left frontal headaches, sweats and right anterior chest pain of pleuritic type with mild nonproductive cough. He entered the hospital four days after the onset of symptoms. He was acutely ill. The only findings of note were occasional crackling rales at the right lung base posteriorly and in the right axilla. The temperature was 103.8 F. rectally.

A roentgenogram of the chest showed infiltration at the right lung base medially. One month later this showed complete resolution. The blood count was within normal limits. The urine contained albumin (2 plus). This observation disappeared during convalescence. Routine agglutination tests and blood cultures were negative. The results of the complement fixation tests to C. burnetii antigen were as follows: May 31, less than 1:8; June 16, 1:256, and July 26, 1:512. The patient had a daily rise in temperature to 103 F. orally for six days, after which he was afebrile.

CASE 4.—A. G., a white man aged 61, was an attendant of the first patient (case 1) from the time of his admission. Twenty-two days later (May 30) he had a fever (102 F. orally), retrobulbar headaches, chills, sweats and a mild, nonproductive cough. He was ill at home for a week but did not seek medical care. After his return to work the connection between his illness and the other cases was suspected, and a complement fixation test for Q fever was performed July 25. It was positive in a 1:64 serum dilution. A specimen taken September 6 was

10. All complement fixation tests with the C. burnetii antigen were performed at the Viral and Rickettsial Disease Laboratory, Division of Laboratories, California State Department of Public Health, 1392 University Avenue, Berkeley 2, Calif.

anticomplementary. Although a diagnosis of Q fever cannot be made on the basis of the serologic test alone, and since a rise in titer was not demonstrated, the diagnosis has been made because of the clinical symptoms, exposure to the first patient, the positive serologic test and the onset of illness concurrent with the other cases.

SUMMARY

1. A case of Q fever with apparent transmission of the disease to 3 other persons is reported.

2. The mode of transmission was not determined.

BETA-GLUCURONIDASE STUDIES IN WOMEN

I. Observations in 500 Nonpregnant, Noncancerous Subjects

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The increasing interest in the beta-glucuronidase activity of body tissues and fluids in health and disease has made urgent the report of an adequate control series. A systematic study of vaginal fluid and cervical biopsy specimens has been undertaken in this laboratory on several groups of women in an attempt to establish the base line control levels for normal women. The findings and a discussion of the present concepts of their physiologic import are reported in this, the first of our series of papers on this subject. The method for collecting the specimens and the procedure for handling the material will be described in detail, together with an analysis of the results in a study of 500 nonpregnant, noncancerous women.[1] Subsequent papers in this series will deal with additional aspects of the beta-glucuronidase activity of tissues, fluid and venous blood in physiologic and pathologic states in women.

Beta-glucuronidase is an enzyme widely distributed in mammalian tissues, whose function, properties and behavior have recently been reviewed.[2] Experiments with mice [3] and observations in pregnant women [4] have indicated its role in the action and metabolism of estrogenic hormones. It has been found in human cancer tissue [5] in higher concentrations than in healthy tissue in the majority of cases. The presence of a striking difference in the glucuronidase activity of cervical cancer tissue led Odell [6] to state that the glucuronidase activity of the vaginal fluid could be used as a diagnostic aid in detecting cervical cancer. The present data have been collected with a view to making comparisons later with observations on women with treated and untreated cancer of the cervix.

METHOD

The vaginal fluid in the subjects studied in this report was obtained in a simple and standard manner. The specimens were secured before any vaginal examination, whether digital or instrumental, had been made. Lubricating jelly was not used and douches were interdicted for twelve hours before the specimens were obtained. The standard Papanicolaou glass pipet was used, 16 cm. long and 0.6 cm. in diameter, with the distal end polished to reduce the capillary bore to approximately one third of the original diameter. A standard Papanicolaou 2 ounce rubber suction bulb was attached to the dry, clean pipet and the vaginal fluid was obtained by the method used in the cytologic study of exfoliated cells. The bulb is compressed, the pipet inserted high into the posterior vaginal vault and the fluid collected in the pipet by releasing the bulb and slowly sweeping the pipet across the vagina as it is being withdrawn. The fluid is then expelled from the pipet by means of the bulb into carefully weighed, standard Wassermann tubes, 10 cm. long and 1.3 cm. in diameter, marked with a diamond point pencil for identification. There is usually sufficient material in the pipet for the preparation of slides for the cytologic study of exfoliated cells. This procedure was carried out with the majority of specimens as an additional control and to assist in interpretation of the findings. The specimens were usually kept at 4.0 C. until the analysis was made.

The weight of the tube with the vaginal fluid specimen was recorded, and the contents were well mixed by means of a close-fitting glass rod attached to a rotating electrical motor shaft. A total of 3 cc. of tenth-molar acetate buffer (p_H 4.5) was employed. The glucuronidase activity of such suspensions of vaginal fluid was found to remain stable in the cold for at least twenty-four hours. Values obtained on specimens below 5 mg. in weight were regarded as unreliable and discarded. As a rule specimen weights ranged between 10 and 50 mg., and, even with amounts of approximately 100 mg., valid results, as proved by multiple samples, were obtained.

The use of an immunologic pipet for sampling vaginal fluid was found to be impractical. In only 1 of 4 women could sufficient fluid material be obtained, and variation in the consistency rendered uncertain the exact amounts actually being assayed for enzyme activity. The inside of the pipet would often be coated with sticky secretions, simulating a false fluid volume level.

From the well suspended homogenate, 0.1 cc. portions were pipetted first into two Wassermann tubes containing 0.8 cc. of tenth-molar acetate buffer (p_H 4.5) and 0.1 cc. of hundredth-molar phenolphthalein glucuronide and then into a third tube containing 0.8 cc. of tenth-molar acetate buffer. These tubes were incubated overnight at 38 C., and the reaction was stopped after the time had been recorded by placing the digests in boiling water for one minute. This procedure of deproteinizing was more satisfactory than trichloracetic acid precipitation. One and five-tenths cubic centimeters of water were added, and, after centrifuging, 2.0 cc. of each of the supernatants were transferred to Evelyn cuvettes, 2.5 cc. of alkaline glycine reagent,

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Miss Margit Olsen, of the Cytology Laboratory, New England Center Hospital, read the smears in this study.

From the Cancer Research and Cancer Control Unit of the Department of Surgery and the Departments of Medicine and Biochemistry, Tufts College Medical School, Boston.

This study was aided by grants from the United States Public Health Service, the American Cancer Society, Inc., New York, and the Damon Runyon Memorial Fund for Cancer Research, New York.

1. The subjects were obtained from the Tumor Clinic of the Boston Dispensary, the New England Center Hospital, the Holy Ghost Hospital, the Jewish Memorial Hospital and from the private patients of one of us (S.C.K.).

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6. (*a*) Odell, L. D., and Burt, J. C.: β-Glucuronidase Activity, Science **109**: 564, 1949. (*b*) Odell, L. D.; Burt, J. C., and Bethea, R.: β-Glucuronidase Activity in Human Female Genital Cancer, Cancer Research **9**: 362, 1949.

1 cc. of 5 per cent trichloracetic acid and water to complete the 6 cc. volume were then added, in the order given. The reading of the optical density and calculation of results were performed exactly as described previously,[7] taking into account that 2 cc. of a total of 2.5 cc. were taken for color development.

Tissue specimens were collected in weighed tubes, homogenized in acetate buffer and assayed for glucuronidase activity. Multiple specimens of vaginal fluid or of degenerating cervical cancer may sometimes show a variation as great as 50 per cent. Accordingly, whenever possible, we have taken duplicate specimens of fluid and tissue. A number (106) of cervical biopsy specimens have been assayed for beta-glucuronidase activity, which has been correlated with the histologic state of the tissue.

RESULTS

A total of 500 nonpregnant women without clinical, cytologic or pathologic evidence of cancer have been studied for this report. The age distribution of these subjects is uniform and follows closely the standard age distribution, from the age of 40 years upward, for women in the Commonwealth of Massachusetts (fig. 1). The glucuronidase values have been recorded for statistical purposes, first in ranges of 300 to 900 units and then at levels of 1,500 to 4,500 units. These points for analysis were arbitrarily chosen in order to make possible convenient comparisons of these data with that on cancer subjects.

These women have been divided arbitrarily into age groups of 20 to 40, 41 to 60 and 61 to 90 years. The

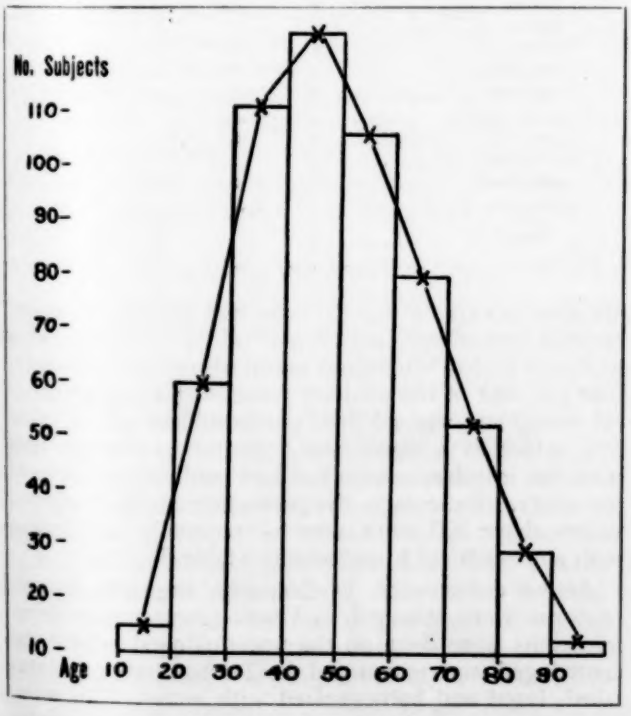

Fig. 1.—Age distribution.

percentage of specimens studied in women of each age group has been related to beta-glucuronidase activity in figure 2. It will be noted that the range of beta-glucuronidase activity falls between 0 and 4,500 units in noncancerous, nonpregnant women. It is especially noteworthy that an attempt to establish, in vaginal fluid evaluation, a critical value for cancer set arbitrarily at either 300 or 600 units would of necessity be difficult. It can be seen from table 1 that 65.3 per cent of the total number of observations made show values below 300 units. An additional 15.3 per cent of observations show values between 300 and 600 units. The remaining 19.4 per cent show values between 600 and 4,500 units.

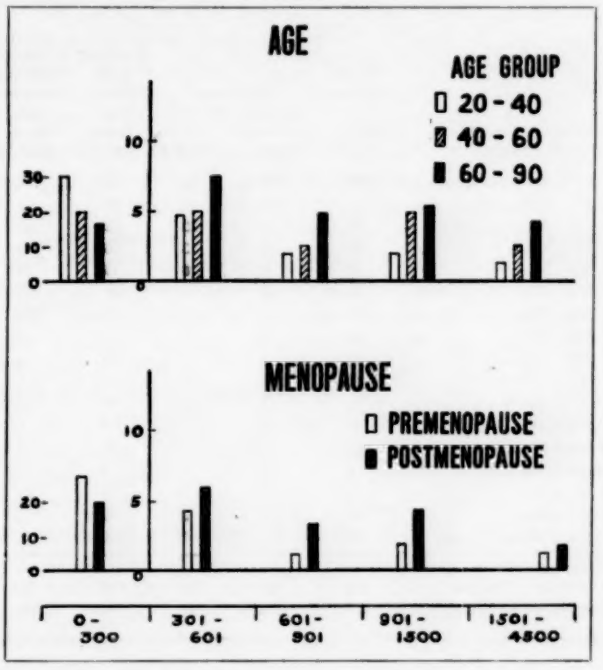

Fig. 2.—Relationship of the percentage of specimens studied in each age group to the beta-glucuronidase activity. The horizontal line of figures at the bottom represents the beta-glucuronidase activity of the vaginal fluid, while the vertical line of figures at the left represents the percentage of total observations.

The significant aspect of figure 2 is the strong tendency for women over 40 years of age to make up an increasingly greater proportion of the values over 300 units. When the subjects are divided into premenopausal and postmenopausal groups, this tendency for increase in proportion at the higher levels is accentuated. Of the 500 women, 168 were postmenopausal subjects. In 51 of these the menopause had been surgically induced. In the majority of the remaining subjects the physiologic menopause had occurred between the ages of 48 and 52 years, a level consistent with the standard age for the menopause in this climate. In table 2 the data on women before and after the menopause have been related to age.

The results of examination of exfoliated material from vaginal fluids, aliquots of which were studied for β-glucuronidase activity, are shown in table 1. The classification suggested by Papanicolaou was used in grading the cytologic smears. Class 1 represents the completely normal cytologic smear. Class 2 represents the unquestionably benign smear which has some aberrations from the normal, such as an excessive number of pus cells, aberrant normal cells and atypical estrogen levels for the expected physiologic normal in the subject studied.

Classifications higher than 2 were not encountered in this study, since in no instance were suspicious or frankly cancerous smears found. Of the 323 cytologic smears which were class 1, a total of 237 (73.5 per cent) were found in patients with beta-glucuronidase values below 300 units. On the other hand, 44 (36.5 per cent) of a total of 120 smears which were class 2 were from patients with a range of up to 300 units for beta-

7. Fishman, W. H.; Springer, B., and Brunetti, R.: Application of an Improved Glucuronidase Assay Method to the Study of Human Blood β-Glucuronidase, J. Biol. Chem. **173**: 449, 1948.

glucuronidase activity. This suggests a study of the relationship between the presence or absence of gynecologic complaints in these women, and these data are given in the last section of table 1. The discrepancy between the total number of subjects studied and the number of beta-glucuronidase values recorded is due to the fact that several specimens were obtained from some persons, and every specimen was given equal weight in the analysis of results.

TABLE 1.—*Facts Related to the Distribution of Glucuronidase Values of the Vaginal Fluid*

Beta-Glucuronidase Units	No. of Studies of Vaginal Fluid	No. of Studies of Exfoliated Cells		No. of Patients with Gynecologic Complaints	No. of Patients Without Gynecologic Complaints
		Class 1	Class 2		
0- 100	247	143	15	69	178
101- 200	115	62	13	39	76
201- 300	66	32	16	32	34
301- 400	45	18	10	16	29
401- 500	23	8	6	13	10
501- 600	35	13	13	19	16
601- 700	15	5	6	10	5
701- 800	15	4	5	9	6
801- 900	13	8	4	9	4
901-1,000	17	6	2	9	8
1,001-1,500	30	12	13	20	10
1,501-2,000	14	9	2	9	5
2,001-2,500	13	1	8	11	2
2,501-3,000	2	1	1	2	...
3,001-3,500	4	1	2	4	...
3,501-4,000	2	...	3	2	...
4,001-4,500	2	...	1	2	...
Total number of observations	658	323	120	275	383
Number of patients	500	...	443	174	326

TABLE 2.—*Relation of Frequency of Observations to Age, the Menopause and Beta-Glucuronidase Activity in Noncancerous, Nonpregnant Women*

Units *	21-40 Years	Premenopause 41-60 Years	Postmenopause 41-60 Years	61-90 Years
0- 50	69	22	28	25
51-100	41	18	24	27
101-150	18	10	11	18
151-200	16	14	11	18
201-250	10†	8	17	5
251-300	5	1	10	10
301-350	5	2	1	8
351-400	3	4†	9	9
401-450	2	2	2	1
451-500	3	1	2	4
501-550	3	2	4	7
551-600	1	3	6	7
601-650	1	0	1	4
651-700	2	0	2	5
701-750	0	0	1†	2
751-800	1	1	4	6†
801-850	2	1	2	0
851-900	0	2	3	2
901-950	0	2	2	1
951-1,000	2	2	3	3
1,000 and up	6	3	19	30
Total number	190	98	162	192

* The mean beta-glucuronidase values in the age group of 21 to 40 years was 192 units; in the age group of 41 to 60 it was, premenopause, 300 units and, postmenopause, 526 units, and in the age group of 61 to 90 it was 508 units.

† Level below which 80 per cent of women in the age group are found.

It will be noted that 51.0 per cent of the 275 observations in patients with clinical gynecologic complaints showed beta-glucuronidase values of less than 300 units. Women without clinical gynecologic complaints who had beta-glucuronidase values below 300 units represent 75 per cent of a total of 383 observations. Patients with frank clinical or laboratory evidence of Trichomonas vaginalis infection are included in the group with gynecologic complaints. There is a tendency, noted in the sections on exfoliated cells and gynecologic complaints of table 1, for the presence of aberrations from the cytologic and clinical normal to be associated with values above 300 units.

In view of the statement [6b] that the presence of blood in the vaginal fluid reduces its glucuronidase activity, it should be noted that our data do not include appreciable numbers of sanguineous specimens.

The 79 observations on women who have undergone hysterectomy were divided into two groups, one of 46 observations on women who had undergone supracervical procedures and another of 33 observations on women who had undergone panhysterectomy. Seventy-four per cent of the subjects possessing a uterine cervical stump had vaginal fluid glucuronidase values below 300, which is a significantly greater percentage than occurred in subjects who had had panhysterectomy (43 per cent). Patients in the panhysterectomy group had values above 300 units twice as frequently as did those with supracervical hysterectomy (table 3).

TABLE 3.—*Relationship Between Beta-Glucuronidase Activity in the Vaginal Fluid and Hysterectomy*

Beta-Glucuronidase Units	Supracervical Hysterectomy		Panhysterectomy	
	No.	%	No.	%
0-100	18	39.2	6	18.0
101-200	7	15.3	5	15.0
201-300	9	19.5	3	10.0
301-400	3	6.5	1	3.0
401-500	1	2.1	2	6.0
501-600	1	2.1	2	6.0
601-700	1	2.1	1	3.0
701-800	..	....	..	6.0
801-900	1	2.1	2	....
901-1,000	1	2.1	2	6.0
1,001-1,500	2	4.2	4	12.0
1,501-2,000	..	....	2	6.0
2,001-2,500	1	2.1	..	....
2,501-3,000	..	....	1	3.0
3,001-3,500	1	2.1	2	6.0
3,501-4,000	..	....	..	....
Total	46		33	

Active cultures of Trichomonas vaginalis hominis protozoa were obtained, and beta-glucuronidase determinations were done on the uncentrifuged culture, the centrifuged supernatant and the Trichomonas organisms laked, lysed and homogenized with water. The activities of the uncentrifuged and centrifuged cultures were identical with those found in the sterile medium itself (which contains a slight amount of enzyme derived from the human serum present). The laked organisms showed no beta-glucuronidase activity whatsoever. Vaginal fluid specimens taken at intervals of several days over a period of months in regularly menstruating women showed cyclic changes in the glucuronidase activity.

Results of glucuronidase assays in 8 pregnant women showed a range of values from 0 to 1,930 units of

activity, with 3 above 300 units and 5 showing less than 300 units of activity. It is apparent from this small number of studies that pregnancy does not uniformly result in a high glucuronidase activity in the vaginal fluid.

COMMENT

A suitable control series of observations is essential for the proper interpretation of beta-glucuronidase values obtained in cancerous and benign conditions. It is felt that 500 nonpregnant, noncancerous subjects are an adequate number for statistical analysis. It has been reported that in the pregnant state the beta-glucuronidase values in the vaginal fluid are elevated.[8] Since pregnant women were not included, our incidence of high beta-glucuronidase values is lower than it would have been in a series including both pregnant and nonpregnant women. Another factor, the presence of T. vaginalis infection, stated to account for high vaginal glucuronidase values, was operative in an undetermined number of our subjects.

Recent information indicates that 68 per cent of women who show no T. vaginalis in the hanging drop preparation reveal the presence of the protozoa in culture preparations.[8] On this basis, the total incidence in women of T. vaginalis infections may approximate 80 per cent. Accordingly, the presence or absence of these infections may well have a limiting effect on the incidence of high values. In our experience, both low and high values have occurred in the presence of frank T. vaginitis infection. Since active pure cultures of the motile protozoa and the lysed organisms themselves contain no appreciable amount of the beta-glucuronidase enzyme, the impression is strengthened that the part played by the Trichomonas organisms in some of the high values encountered is of less importance than has been implied.[6] Nevertheless, a search should be made into the mechanisms by which the presence of Trichomonas in the vagina may influence the beta-glucuronidase activity of the vaginal fluid, a problem under investigation.

The age distribution in this series is sufficiently wide to offer an over-all picture of the glucuronidase values to be expected in any age group from 20 to 90 years. The subjects have been divided into three age groups, 20 to 40, 41 to 60 and 61 to 90 years, so that the age group in which cancer of the genital tract in women is most frequent (41 to 60) could be delineated.

The data have been grouped in multiples of 300 units not only for statistical evaluation but also because the value of 312 units was stated to be the one which divided patients with cervical cancer from those without it.[6b] The range of values for all observations is great, from 0 to as high as 4,500 units per gram of vaginal fluid. The group having the predominant number of values below 300 units is made up of women aged 20 to 40. Since these women represent 40 per cent of the total number studied, an appreciable number (52) have values greater than the arbitrary level of 300 units. Women in the age group in which cancer of the genital tract is most frequent (41 to 60) and particularly those above it had the majority of the values above 300 units. This suggests that the origin of vaginal glucuronidase enzyme has some relation to the process of aging.

It should especially be noted that the age groups in which genital cancer is prevalent are those in which noncancer controls have higher values. Thirty-four per cent of the 658 observations showed values higher than 300 units. If this arbitrary level is used as a dividing line for the diagnosis of cervical cancer, one third of the female population would fall into this category. The inclusion of pregnant women would only serve to increase this figure. Other significant data may be computed from figure 2. Thus, 77 per cent of women in the age group 20 to 40, 59 per cent in the group 41 to 60 and 43.5 per cent in the group 61 to 90 have vaginal fluid values below 300 units per Gm.

With regard to the menopause, there is a significantly greater incidence of high beta-glucuronidase values in the vaginal fluid in women after the menopause. As the beta-glucuronidase level increases, postmenopausal women predominate to a noticeable extent, which is consistent with the relationship to age discussed previously. Of the total number of women in the 41 to 60 age group (260), 98 were premenopausal and 162 postmenopausal. The principal difference in these two groups is the functional state of the ovaries, and it is interesting to note that women in this age group after the menopause average 525.6 units and before menopause 299.7 units of activity per gram of vaginal fluid. In this respect, in a total of 11 patients who had undergone bilateral oophorectomy, the average value for glucuronidase activity in the vaginal fluid was 1,110 units, with a range of 0 to 3,460. All these considerations are suggestive of a role for the functioning ovary in determining the glucuronidase activity in the vaginal fluid.

It is too early to attach a great deal of significance to the numeric averages, since the figures include values over 1,000 units in appreciable numbers, while the bulk of the data is found below 300 units. However, it is possible to establish values from table 2, from which one may predict from our present data the level below which 80 per cent of women in a given age group would fall. These values, we feel, may be employed as tentative standards for making comparisons with the glucuronidase activity in the vaginal fluid in varying groups of women.

It should be noted that the 80 per cent level in women aged 20 to 40 is at most 250 units; in those aged 41 to 60, premenopausal, 400 units, and postmenopausal, 750 units, and in those aged 61 to 90, 800 units. The most significant aspect of these data is that if 300 units were taken arbitrarily as the level which divides, with 80 per cent accuracy,[9] those women without cancer from those with the disease, a gross error would be evident in women over 40 after the menopause.

Cytologic studies of exfoliated material are being used to advantage in identifying early cancerous lesions of the genital tract which might escape identification by clinical examination. False negative results in patients with cancer of the cervix make up not more than 10 per cent of the results reported by a number of investigators.[10] The experience of our cytologic laboratory is consistent with these findings. The fact that in no

8. Williams, M. H.: A Study of the Trichomonad Population in Experimentally Infected Rhesus Monkeys: I. The Efficiency of Intensive Microscopic Search Compared to Culture Technique, Am. J. Obst. & Gynec., to be published.

9. Dieckmann, W. J.: in discussion on Graham, R .M., and Meigs, J. V.: The Value of the Vaginal Smear, Am. J. Obst. & Gynec. **58**: 849, 1949.

10. Gates, O., and Warren, S.: A Handbook for the Diagnosis of Cancer of the Uterus by the Use of Vaginal Smears, Cambridge, Mass., Harvard University Press, 1947, pp. 51-52. Graham, R. M., and Meigs, J. V.: The Value of the Vaginal Smear, Am. J. Obst. & Gynec. **58**: 843, 1949.

instance was a positive cancer smear observed independently in 443 subjects eliminates for all practical purposes the possibility that an appreciable number of our high values of beta-glucuronidase activity in the vaginal fluid were due to unsuspected and undiscovered cancer of the cervix. We have found the cytologic study of exfoliated material indispensable for the evaluation of these data.

The difference between those subjects wth gynecologic complaints and those without gynecologic complaints in respect to the level of beta-glucuronidase activity in the vaginal fluid is not of sufficient magnitude to warrant interpretation. This appears to make the selective value of gynecologic complaints unsatisfactory as the sole criterion for the use of beta-glucuronidase determinations in subjects who may have cancer. Additional study of the parts played by the ovary and the pituitary and adrenal glands, as well as cultural diagnostic study of Trichomonas, may serve to clarify, in cytologic and clinical studies, aberrations from the normal found to be frequently associated with beta-glucuronidase values in the vaginal fluid above 300 units.

Elimination by surgical means of the uterine corpus, with or without the cervix, offers some insight into the source of vaginal fluid glucuronidase. The range of values (table 3) falls between 0 and 3,500 units. Especially noteworthy is the fact that patients in whom the entire uterus and cervix have been ablated make up a significantly larger proportion of the group with values above 300 units. This signifies clearly that the presence of the uterine corpus and cervix are not fundamentally essential for the presence of high enzyme values. The part played by the presence of ovarian tissue in the group of women who had undergone hysterectomy is of great significance and should be further evaluated.

TABLE 4.—*Beta-Glucuronidase Activity in Benign Uterine Cervix*

Patient	Units/ Gm.*	Patient	Units/ Gm.*	Patient	Units/ Gm.*	Patient	Units/ Gm.*
B. R.	151	D. R.	11	K. A.	150	R. A.	60
B. D.	130	E. F.	181	K.	32	T.	341
B. B.	170	F. M.	200	K. M.	178	T. S.	99
B. E.	334	G. P.	0	L. E.	116	W. M.	145
B. M.	92	G. R.	533	M. N.	210	W. B.	219
B. R.	250	G. R.	22	N. S.	203	W. K.	97
C. C.	157	G. R.	286	R.	257	Z. S.	161
C. M.	0	G. S.	138	S. M.	193		
C. S.	240	H.	77	S. M.	39		
D. C.	52	H. E.†	31, 30,	S. A.	110		
D. B.	165		30, 67,	S. R.	126		
D. B.	92		32	R. G.	212		
D. N.†	328, 364,	I. H.	156	R. E.	83		
	429, 189	J. O.	27				

* The average was 153 units of activity per gram of fluid. The range of activity was 0 to 533 units.
† Multiple specimens.

With respect to the beta-glucuronidase activity of cervical tissue, the group with cervical cancer has shown a much higher level of the enzyme, as compared with the control group (tables 4 and 5). It is of interest to note that specimens obtained beyond the gross limits of cervical cancer have beta-glucuronidase values falling well below 300 units. Biopsy specimens obtained in the same subjects from the cancerous lesion universally showed values above 500 units (table 5). In but one instance of 45 was there a value higher than 500 units in tissue obtained from the benign cervix. This would lead us to believe that the study of glucuronidase activity in vaginal fluid must be evaluated separately from similar studies carried out on biopsy specimens. Recent histochemical studies corroborate the characteristic high beta-glucuronidase values in cancerous tissue.[11]

TABLE 5.—*Beta-Glucuronidase Activity in Untreated Cervical Cancer*

Patient	Units/Gm.* Involved†	Uninvolved‡	Patient	Units/Gm.* Involved†	Uninvolved‡
A. V.§	1,745, 2,470		P. A.	644	
A. M.	765		R. M.	2,020	339
C. C.	555	58	S. M.	1,375	138
D. A.	641		T. A.	1,510	
D. H.§	820	51, 95, 50	W. C.	595	
F. C.§	1,660, 720		R.§	793, 1,021	
G. M. E.	1,175			682	
M.§	820, 1,510		M. H.§	1,120, 5,950	
M. S.§	3,810, 3,320			926, 1,600	
	2,280, 2,450		V. F.§	1,510, 1,000	
	2,360, 1,245			1,390	
	2,020, 2,915		B. R.§	700, 1,920	
M. A.	1,610			1,640, 2,319	
M. M.	2,350			2,880, 648	
P. L.	1,103		F. V.§	2,016, 930	
				1,510, 2,130	

* The average was 1,647 units of activity per gram of fluid. The range of activity was from 555 to 5,950 units.
† The heading "Involved" indicates that the source of the specimens was typical cancerous tissue obtained in a biopsy of the uterine cervix.
‡ The heading "Uninvolved" indicates that biopsy specimens were obtained, in the same patients, outside the limits of the gross cancer tissue in the cervix.
§ Multiple specimens.

In the course of this study, we have encountered several pitfalls which deserve mention. Uniformity in the sampling technic is important, and duplicate specimens should be analyzed whenever possible. The weight of the specimen has been found much more dependable than the volume as a basis of expressing the results. A minimum degree of handling and treatment of the material is desirable.

SUMMARY

Five hundred nonpregnant, noncancerous women were studied with regard to beta-glucuronidase activity in vaginal fluid and, in 45 of these, in cervical tissue. The age group into which subjects fall is of importance in interpreting the incidence of high values (those above 600 units). Women after the menopause from ages 41 to 60 possess high values twice as frequently as do subjects aged 20 to 40. The relevance of ovarian function in this phenomenon may be indicated by the presence of higher values in women who have completed the menopause and in women who have undergone oophorectomy. Living Trichomonas vaginalis organisms themselves do not possess the enzyme beta-glucuronidase. From the study, it is clear that factors in addition to pregnancy, such as T. vaginalis infection and cancer, are implicated in the evaluation of high beta-glucuronidase activity in the vaginal fluid.

The uniform incidence of elevated glucuronidase activity in cervical cancer tissue is a striking phenomenon, and its significance will be evaluated separately from the vaginal fluid study.

11. Seligman, A. M.; Nachlas, M. M.; Manheimer, L. H.; Friedman, O. M., and Wolf, G.: Development of New Methods for the Histochemical Demonstration of Hydrolytic Intracellular Enzymes in a Program of Cancer Research, Ann. Surg. **130**: 333, 1949.

ALCOHOL IN THE TREATMENT OF ANGINA PECTORIS

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FREDERIC D. REGAN, M.D.
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Alcohol has been regarded as a valuable drug in the treatment of angina pectoris since the earliest description of the disease by Heberden [1] in 1786. It is rated by most contemporary authorities as one of the few effective coronary vasodilators, second only to the nitrites.[2] Indeed, the effect of 1 or 2 ounces (30 to 60 cc.) of whisky or brandy in terminating an anginal attack is said to be comparable in many instances to the results obtained with glyceryl trinitrate. Nevertheless, it is in the prevention rather than in the treatment of these episodes that alcohol has been deemed of particular clinical value.[2b] Physicians frequently prescribe it in angina pectoris as a routine prophylactic measure and especially before contemplated effort or excitement.

In spite of such wide therapeutic endorsement, surprisingly little is known regarding the actual effect of alcohol on disturbances of coronary blood flow in human disease. The observed influence of the drug on anginal pain has been almost universally accepted as proof of its coronary vasodilating action. Experimental evidence, however, does not support this contention. Various investigators [3] have failed to observe a significant increase in coronary blood flow in animals even with high concentrations of the drug. It seems possible, therefore, that another mechanism may be responsible for the symptomatic relief frequently afforded by this agent.

Alcohol has long been known to be a depressant of the central nervous system capable of decreasing anxiety and promoting a sense of well-being.[4] Its beneficial influence in angina pectoris may therefore arise from its sedative action, through which it increases the threshold for pain sensation without exerting any significant effect on underlying myocardial anoxia. If this hypothesis is established the indications for the use of alcohol in coronary disease will require reevaluation. The employment of a drug which prevents the warning stimulus of pain without influencing the actual status of the coronary circulation obviously presents a theoretic hazard in prophylactic therapy. Although such a drug may have some value in the treatment of the anginal attack it cannot accurately be classed with the nitrites, which have been shown to reverse the electrocardiographic pattern frequently observed during transient episodes of coronary insufficiency.

Other authors have attempted to evaluate the effect of alcohol in the treatment of angina pectoris, utilizing pain alone as an index of myocardial ischemia. Evans and Hoyle [5] studied records covering two week periods during which patients noted the number of attacks, the duration of pain and the effect of medication. Stearns, Riseman and Gray,[6] on the other hand, endeavored to measure the influence of alcohol on exercise tolerance by having their patients continuously ascend and descend a two step staircase in a cold room until angina developed. Such technics would be acceptable for assaying the vasodilator potency of drugs if pain represented a definite end point and reflected a fairly constant degree of coronary insufficiency in the individual patient. Obviously, however, this is not the case. Pain is of infinite variability and to date has not been accurately quantitated in man either subjectively or objectively. Furthermore, even if such precise measurement were possible, pain could not reliably reflect the status of the coronary circulation. In our laboratory, for example, patients showing quantitatively constant electrocardiographic alterations with each performance of a standard exercise test under carefully controlled conditions have experienced no distress on some occasions and appreciable pain on others.

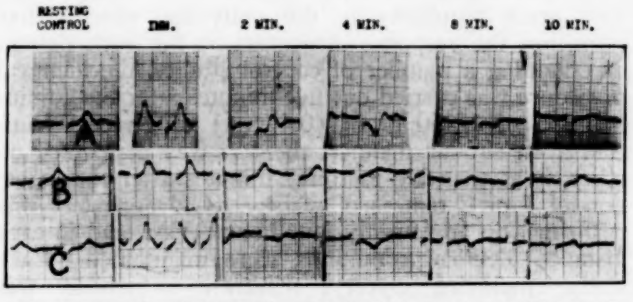

Fig. 1 (case 1).—Electrocardiograms (lead 4) showing modifying influence on resting control of standard exercise (Master two-step test[8]) after a certain time interval (minutes between medication and beginning of test). In all figures response *A* follows no medication, no time interval; response *B* follows 1/150 grain (0.4 mg.) glyceryl trinitrate orally, time interval five minutes. In figure 1 response *C* follows 45 cc. whisky orally, time interval twenty minutes.

Conversely, as Dock [7] has pointed out, "a minute ischemic area in the myocardium may cause as severe discomfort as ischemia of a whole ventricle." Consequently, if the action of alcohol is to be critically analyzed, a more accurate index of coronary insufficiency is required than that afforded by the sensation of pain alone.

At the present time electrocardiography offers the most objective means of evaluating changes in coronary circulation. It is significant, furthermore, that certain patients with coronary disease repeatedly show transient RS-T segment depression and T wave inversion of constant pattern in response to standard exercise.[8] In such selected cases it is possible to determine accurately the modifying action of various drugs on the electrocardiographic response to measured exercise. Accordingly, a technic was devised in which alcohol and glyceryl trinitrate could be compared objectively with regard to their effectiveness in preventing previ-

As a joint project with the National Heart Institute, United States Public Health Service, Washington, D. C.

From the Cardiovascular Research Unit, Department of Medicine, United States Marine Hospital, Staten Island, N. Y.; consultant in cardiovascular disease (Dr. Russek).

1. Heberden, W.: Some Account of Disorder of Breast, M. Tr. Roy. Coll. Physicians **2**: 59, 1786.

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3. Dixon, W. E.: Action of Alcohol on Circulation, J. Physiol. **35**: 346, 1907. Sulzer, R.: Influence of Alcohol on Isolated Mammalian Heart, Heart **11**: 141, 1924. Gilbert, N. C., and Fenn, G. K.: Effect of Purine Base Diuretics on Coronary Flow, Arch. Int. Med. **44**: 118 (July) 1929.

4. (*a*) Jetter, W. W.: Chemical and Clinical Diagnosis of Acute Alcoholism, New England J. Med. **221**: 1019, 1939. (*b*) Miles, W. R., in Emerson, H., and others: The Psychologic Effect of Alcohol in Man, New York, The Macmillan Company, 1932. (*c*) Goodman and Gilman.[2a]

5. Evans, W., and Hoyle, C.: Prevention and Treatment of Individual Attacks of Angina Pectoris (Angina of Effort), Quart. J. Med. **3**: 105, 1934.

6. Stearns, S.; Riseman, J. E. F., and Gray, W.: Alcohol in the Treatment of Angina Pectoris, New England J. Med. **234**: 578, 1946.

7. Dock, W.: Angina Pectoris, The Neuralgic Features of the Classic Form of Heberden's Disease, M. Clin. North America **33**: 635, 1949.

8. Russek, H. I.; Smith, R. H.; Baum, W.; Neagle, C., and Regan, F. D.: Influence of Saline, Papaverine, Nitroglycerine and Ethyl Alcohol on the Electrocardiographic Response to Standard Exercise, Circulation **1**: 700, 1950.

ously observed patterns of myocardial ischemia in suitable test cases.

Method.—As a result of screening a large number of patients with angina pectoris by means of the Master two-step test,[9] 5 cases were found in which the electrocardiographic response remained constant when

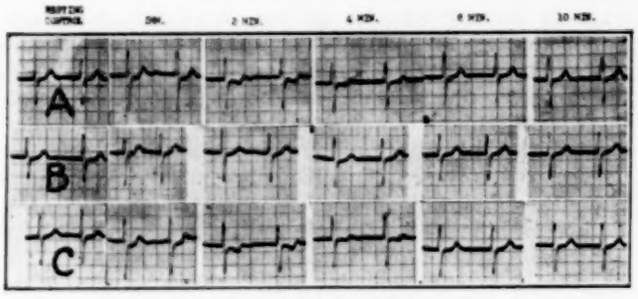

Fig. 2 (case 2).—Electrocardiograms (lead CF_4) as in figure 1, except that response *C* follows 30 cc. of whisky orally, time interval ten minutes.

recorded from day to day. Thus in each of these cases a constant pattern of change was repeatedly observed in the tracings taken during the ten minute interval following exercise. These transient electrocardiographic changes, moreover, appeared and disappeared with great regularity in the individual case. After recording the response characteristic for each patient by obtaining a number of control studies, the identical procedure was carried out five minutes after the administration of 1/150 grain (0.4 mg.) of glyceryl trinitrate. In similar manner, the test was performed on other occasions, five to thirty minutes after the ingestion of 1 or 2 ounces of whisky. Only one test was performed in any twenty-four hour period, and in each instance identical conditions were maintained. Each study employing glyceryl trinitrate or whisky was repeated at least once, and additional control records were obtained at frequent intervals throughout the period of observation.

Results.—The control electrocardiograms recorded after exercise in each of the cases studied show transient changes in the RS-T segments and T waves which according to accepted standards, are clearly indicative of myocardial ischemia.[10] Thus in each of these cases exercise was followed by depression of the RS-T segment (amounting to considerably more than 0.5 mm.)

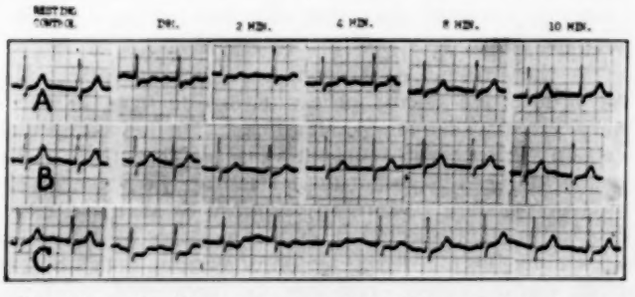

Fig. 3 (case 3).—Electrocardiograms (lead CF_4) as in figure 1, except that response *C* follows 60 cc. of whisky orally, time interval five minutes.

and flattening or inversion of the T wave. When glyceryl trinitrate (1/150 grain, sublingually) was administered to each of the patients five minutes before the beginning of the test, these changes either completely failed to appear or were minimal in nature. In every instance there was a decided difference between the control records and those obtained after premedication with glyceryl trinitrate (figs. 1 to 5, inclusive). In striking contrast, the administration of 1 or 2 ounces of whisky five to thirty minutes before the test exerted little or no influence on the electrocardiographic response to standard exercise. Thus it is evident from the tracings that alcohol was without significant effect in preventing the RS-T changes induced by this standard procedure (figs. 1 to 5).

In spite of these pronounced differences, whisky did appear comparable to glyceryl trinitrate in its ability to prevent the onset of anginal pain during the performance of the exercise test.

COMMENT

The results of this study clearly indicate that a misconception exists regarding the value of whisky in the treatment of coronary disease. Although this agent is

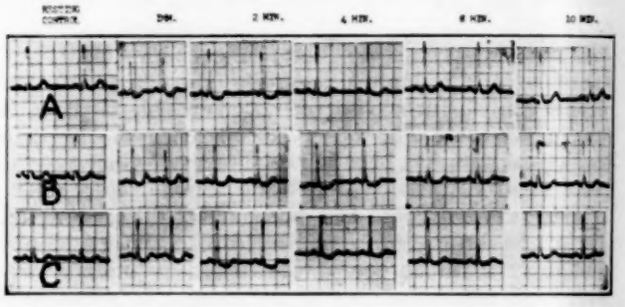

Fig. 4 (case 4).—Electrocardiograms (lead 1) as in figure 1, except that response *C* follows 60 cc. of whisky orally, time interval ten minutes.

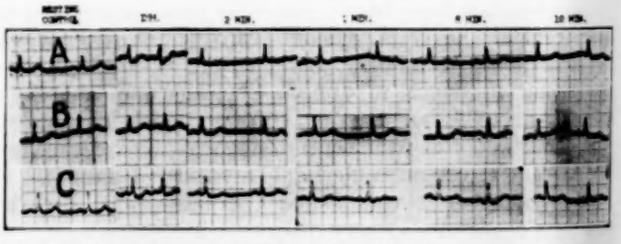

Fig. 5 (case 5).—Electrocardiograms (lead 1) as in figure 1.

capable of preventing an anginal attack or terminating it when present in many patients, the clinical effect of the drug appears to result from an action independent of coronary vasodilatation. Thus, in the cases herein reported whisky completely failed to prevent the electrocardiographic patterns of myocardial ischemia induced by standard exercise. Since its pharmacologic action on coronary circulation differs decidedly from that of glyceryl trinitrate and actually appears insignificant as revealed by this study, alcohol can no longer be accepted as a coronary vasodilator.

Evidence has not yet clearly established whether glyceryl trinitrate acts through specific coronary vasodilatation, lessening of cardiac work or diminution in myocardial oxygen consumption. It seems apparent, nevertheless, that the drug influences anginal pain by tending to correct or prevent the underlying myocardial anoxia which provokes the clinical attack, whereas alcohol does not. Consequently, the view that a glass of whisky is the equivalent of a glyceryl trinitrate tablet for the patient with coronary disease should be rejected.

9. The Master test is a procedure in which the patient ascends and descends a two-step staircase twenty to thirty times, depending on age, sex and weight. Electrocardiograms are recorded immediately after exercise and at two minute intervals thereafter for a period of ten minutes. A depression of the RS-T segment in excess of 0.5 mm. in any of the tracings is regarded as abnormal.

10. Master, A. M., and others: The Electrocardiogram After Standard Exercise as a Functional Test of the Heart, Am. Heart J. 24: 277, 1942.

From these considerations it must be concluded that the action of alcohol in coronary disease is exclusively that of a rapidly acting sedative. Indeed, precisely the same results were obtained in our patients when ¼ grain (15 mg.) of morphine was administered hypodermically twenty minutes before the performance of the exercise tests. It would seem that whisky, like morphine, exerts its effect by greatly increasing central inhibition or suppression of pain sensation. The depressant action of alcohol, even in small dosage, on the function of the higher centers in man is probably responsible for the observed effects of decreasing anxiety, diminishing attention to pain and increasing sense of well-being.[4b]

As desirable as these effects may appear for the patient suffering from an anginal attack, they might prove very undesirable and even hazardous for the coronary patient contemplating moderately severe exertion. Thus the ingestion of whisky by such a person before he undergoes vigorous physical effort may remove not only the protection afforded by angina but also the restrictions imposed by psychogenic influences. Therefore in those instances in which, as a result of the action of this drug, angina either fails to occur or is relieved, effort may be pressed to greater length so that sudden death or a fatal seizure may ensue.

The observations presented justify the conclusion that alcohol is a poor substitute for glyceryl trinitrate. When the latter is not available, however, the subjective comfort and relief of pain frequently provided by alcohol are helpful in the control of the anginal attack. Its sedative action and ability to create a sense of well-being in some patients suggest that it may also have value in the general management of this disease. Nevertheless, inasmuch as the effects of the drug on the central nervous system are not correlated with objective improvement in coronary circulation, its administration in the prevention of attacks may involve appreciable risk. Thus a double danger exists in one's removing the protection afforded by angina while simultaneously imparting a false sense of physical fitness.

SUMMARY

The relief of pain afforded by alcohol in the treatment of angina pectoris has resulted in its wide acceptance as one of the few effective coronary vasodilator drugs. Nevertheless, neither clinical nor experimental evidence thus far advanced lends support to the concept that alcohol augments coronary blood flow.

The present study was undertaken to determine, by means of an objective electrocardiographic technic, whether or not alcohol exerts a modifying influence on the response to exercise in patients with known coronary disease. The results of this investigation may be summarized as follows:

1. Whisky (1 to 2 ounces, 15 to 30 cc.) administered five to thirty minutes before the performance of a standard exercise test failed to prevent the transient electrocardiographic alterations (RS-T depressions and T wave changes) repeatedly observed in the control records of patients with angina pectoris.

2. In sharp contrast, $\frac{1}{150}$ grain (0.4 mg.) of glyceryl trinitrate administered to the same patients five minutes before the performance of the identical test either completely prevented or significantly modified the previously observed patterns of myocardial ischemia.

3. In spite of these differences, whisky appeared as effective as glyceryl trinitrate in preventing angina induced by the standard exercise test.

From these observations, it is concluded that alcohol is not a coronary vasodilator agent. Its role in coronary disease is solely that of a rapidly acting sedative which increases the threshold for pain while promoting a sense of well-being. Consequently, although its sedative and psychogenic action may have value in the general management of the disease and in the treatment of the anginal attack itself, alcohol must be considered a poor substitute for glyceryl trinitrate. Moreover, its employment prophylactically not only may create a false sense of physical fitness but may remove the protection afforded by angina. It would appear that existent views regarding the value of alcohol in the treatment of angina pectoris should be drastically amended.

Clinical Notes, Suggestions and New Instruments

PHENOLSULFONPHTHALEIN TEST FOR TUBAL PATENCY

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During the war years, when apparatus for the determination of tubal patency were not being manufactured, it became imperative that a tubal patency test be devised which would be accurate, simple, safe and economical. Insufflation apparatus of simple construction were suggested in the literature. The Jarcho apparatus, utilizing air, was tried one time, in spite of the fact that its inherent dangers were known. A small air embolus, which produced shock, cyanosis, thready pulse and gasping respirations, developed, but the patient spontaneously recovered after a few minutes. This made the need for a safe tubal patency test even more pressing. Hysterosalpingography is not without dangers and is costly to the patient and inconvenient for both patient and doctor. Thus from necessity was the phenolsulfonphthalein test born.

Phenolsulfonphthalein was chosen because it was considered to be safe, as evidenced by the many years of clinical usage without any reported toxicity. It was further believed that, if it could be given safely by muscular and intravenous routes without being irritating, it probably could be given intraperitoneally without harm.

Determination of the rapidity of absorption of the dye through the peritoneum was necessary, since it was the basis of the proposed test. It was believed that if the dye readily passed through the fallopian tubes and was quickly absorbed and excreted in the urine a simple and visual test for tubal patency could be established. Six milligrams of phenolsulfonphthalein were injected into the peritoneal cavity of 6 rabbit does and the urine collected every five minutes. In each case the dye was recovered from the urine within twenty-five to thirty minutes. Thus it was established that the dye was readily absorbed through the peritoneum of rabbits.

The next step was to see whether or not the dye was easily absorbed through the vaginal mucosa, endocervix, endometrium or endosalpinx. A volunteer was obtained whose tubes had been ligated by the Pomeroy method two years previously. Twelve milligrams of phenolsulfonphthalein diluted to 20 cc. with isotonic sodium chloride solution were placed in the vagina and kept there for two hours. At the end of this time, no dye was recovered in the urine. Then 6 mg. of phenolsulfonphthalein diluted to 10 cc. with isotonic sodium chloride solution were instilled into the uterine cavity. After one hour, no dye was recovered in the urine. Another volunteer was obtained whose tubes were known to be open, and again 6 mg. of phenolsulfonphthalein diluted with isotonic sodium chloride solution to 10 cc. were instilled into the uterine cavity. In thirty minutes, the dye was found in the urine. It was thus felt that phenolsulfonphthalein readily passed through the tubes, entered the peritoneal cavity, was absorbed and passed via the blood to the kidneys, where it was excreted into the urine in an amount sufficient to give a positive reaction to the test. It

was further felt that, if the dye was absorbed at all through the mucosa of the vagina, cervix, uterus or tubes, it was done either slowly, in small amounts, or not at all. Any absorption that occurred did not interfere with the test if the test were completed within thirty minutes.

In June 1948 a preliminary report of this test was published.[1] Twenty-four cases were presented, with an accuracy of 100 per cent. Since then, a known total of 210 cases has been gathered: 45 by me, 55 by Israel[2] and 110 by Palan.[3] The results from these 210 tests were considered accurate in each case. Palan concluded that the test was of clinical value and was reliable. Israel wrote: "The results observed warrant the conclusions that the P. S. P. test is simple, economical and safe, as well as a method of indicating the presence of tubal patency." In none of these 210 cases has there been any unfavorable reaction or evidence of toxicity. Thus, from these several preliminary reports, it can be stated with some degree of assurance that the phenolsulfonphthalein test for the determination of tubal patency is a valuable addition to the armamentarium for the study of human infertility.

INSTRUMENTS

The only instruments necessary are the Grave's speculum, sponge forceps, tenaculum, uterine sound, cannula, 10 cc. syringe, any gage needle, medicine glass, one ampul of phenolsulfonphthalein (6 mg.), isotonic sodium chloride solution, glass catheter, a test tube to collect the urine and 10 per cent sodium hydroxide solution.

TECHNIC

The vagina and cervix are prepared in the same manner as for an insufflation test or hysterosalpingography. All instruments should be surgically sterile. A Grave's speculum is inserted into the vagina. The cervix is grasped with a tenaculum and the cervical canal probed with a uterine sound to determine depth and direction. A cannula (similar to that used with the Jarcho or Rubin apparatus) is inserted into the internal os. The rubber obturator on the cannula fits snugly against the external os and prevents regurgitation. Sterile isotonic sodium chloride solution is poured into a medicine glass. The ampul of phenolsulfonphthalein (6 mg.) is drawn into a 10 cc. syringe and diluted to 10 cc. with the isotonic sodium chloride solution. The needle is removed from the syringe, and the syringe is then inserted into the open end of the cannula. The phenolsulfonphthalein solution is injected slowly into the uterine cavity. The stopcock at the distal end of the cannula is turned so that there will be no reflux of the solution.

If the tubes are closed, or if there is tubal spasm, there will be some resistance to the flow of the solution and the patient will complain of abdominal cramps. If the tubes are patent and the injection is slow, there will be little resistance and little cramping. If there is any leakage about the obdurator, it is readily visible and thus will not interfere with the accuracy of the test—a disconcerting fact, at times, with the Rubin method of insufflation.

The cannula is removed at the end of ten minutes. A tampon is placed in the vagina; the speculum and tenaculum are removed, and the bladder is catheterized. The urine is collected in a test tube to which a few drops of 10 per cent sodium hydroxide solution are added. If the urine turns pink or red, the tubes are considered to be patent. If the urine remains clear, the patient is given a glass of water and twenty minutes later is recatheterized. If the urine remains clear after the addition of 10 per cent sodium hydroxide solution, the tubes are considered to be closed; if the urine is discolored pink or red, the tubes are considered to be patent.

RESULTS

Tubal patency was determined in 45 cases by the phenolsulfonphthalein test. In 24 cases the Rubin test and in 6 cases hysterosalpingography was done with the phenolsulfonphthalein test. In 15 cases, the phenolsulfonphthalein test was done alone. In 10 of these 15 cases the test was confirmed by surgical intervention, and in 1 case the patient subsequently became pregnant. Thus, in all but 4 cases, the accuracy of the phenolsulfonphthalein test was confirmed. The presumptive cause of sterility was oligospermia in 3 of the remaining 4 cases; in the fourth the patient had been sterile since the birth of an only child fifteen years previously, and the result of the phenolsulfonphthalein test was negative.

In the 24 cases in which the Rubin test was made, there were two opposite results. In each case, the result of the phenolsulfonphthalein test was positive and that of the Rubin test negative. However, when the tests were repeated, the results in both tests were positive. This indicated, perhaps, that the false negative result of the Rubin test was due to temporary tubal spasm which had no effect on the phenolsulfonphthalein test. In one test, results of both Rubin and phenolsulfonphthalein tests were positive and hysterosalpingography was reported as revealing closed tubes. This patient became pregnant a few months later. Thus, of 45 determinations, it can be said that the phenolsulfonphthalein test was accurate in 100 per cent of cases; of 24 determinations, the Rubin test was correct in 91.7 per cent, and, of 6 determinations, hysterosalpingography was correct in 83.3 per cent.

CONCLUSIONS

The phenolsulfonphthalein test for the determination of tubal patency is accurate, simple and safe. The test is based on the premise that phenolsulfonphthalein is not easily absorbed (if at all) from the normal vaginal mucosa, endocervix, endometrium or endosalpinx but is readily absorbed from the peritoneal cavity. Thus, if the tubes are patent, the phenolsulfonphthalein will pass from the uterus into the tubes and then into the peritoneal cavity. There it is absorbed, carried to the kidneys and excreted, giving rise to a positive result. (The urine turns pink or red when alkalinized.) If the tubes are closed, this will not occur; the urine will remain clear, and the result of the test will be negative.

2808 S. Randolph Street.

1. Speck, G.: Phenolsulfonphthalein as Test for Determination of Tubal Patency, Am. J. Obst. & Gynec. **55**: 1048 (June) 1948.
2. Israel, S. L.: Personal communication to the author.
3. Palan, F.: Časop. lék. Česk. **88**: 388, 1949.

CARDIOVASCULAR AND RESPIRATORY STUDIES IN PREGNANCY FOLLOWING PNEUMONECTOMY

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J. ROBERT WILLSON, M.D.
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Relatively few pneumonectomies have been performed in women in the childbearing age, the majority of such operative procedures being carried out for pulmonary cancer which occurs most often in men over 40.[1] Because pregnancy following pneumonectomy has not previously been reported, we are reporting the case of a patient who was delivered of a full term infant two years after such an operation. The physiologic changes which occurred incident to the pregnancy, the increased oxygen demand, the increased blood volume and the increased work load on the heart were adequately handled by the cardiovascular and respiratory systems despite a reduction in the size of the pulmonary capillary bed by at least 50 per cent and a loss of more than half the lung parenchyma.

REPORT OF CASE

Mrs. M. O., a white primigravida aged 40, had had her right lung removed at the age of 37 because of grade 1 adenocarcinoma. A year after the pneumonectomy she married, and two years postoperatively, at the age of 39, she became pregnant for the first time. Her last menstrual period began April 29, 1948, and at the first antepartum examination, on July 6, she had no complaints except dyspnea on exertion, which had been present since the pneumonectomy but which had increased somewhat since the onset of the pregnancy. Physical examination at the time showed an apparently healthy woman in no distress. Her blood pressure was 116 systolic and 80 diastolic. Her

From the Departments of Surgery and Obstetrics and Gynecology, Temple University Hospital and School of Medicine.

1. Ochsner, A.; DeBakey, M., and Dixon, J. L.: Primary Cancer of the Lung, J. A. M. A. **135**: 321 (Oct. 11) 1947.

weight was 139 pounds (63 Kg.). There was no distention of the neck veins. There were dulness and absent breath sounds over the right side of the chest. The left side of the chest was clear to percussion and auscultation. The mediastinal structures including the heart were shifted to the right. The heart was apparently not enlarged; the sounds were good and there were no murmurs. Pelvic examination revealed a uterus enlarged to the size of an eight week pregnancy. Pelvic measurements were all within normal limits. There was no ankle edema. Because of the low grade malignancy of the previous pulmonary lesion, the adequate compensation for the loss of the lung and the patient's desire for the baby, the pregnancy was allowed to continue.

The patient was seen at regular intervals throughout the pregnancy, during which her weight increased from 139 to 151 pounds (63 to 68.5 Kg.). Although she complained of increasing dyspnea and attacks of pain in the lower right side of the chest, there occurred no change in blood pressure or pulse rate and no evidence of cardiac decompensation. The urine during pregnancy showed no alteration from normal, and the lowest level of hemoglobin was 11 Gm. per hundred being taken as a point 10 cm. above the skin of the back.[2] Several times during the pregnancy a Caughey [3] cardiac overload test consisting of 1,500 cc. of isotonic sodium chloride solution given intravenously in thirty minutes was performed. The venous pressure was measured at five minute intervals during the administration of the saline solution (i. e., after every 250 cc.) and the vital capacity was measured at the beginning and at the end of the tests. An electrocardiogram was done early in pregnancy and after delivery.

The results of these tests are given in the accompanying table. There was essentially no change in the tidal volume, the vital capacity or the maximum breathing capacity during the course of the pregnancy. There was, however, a slight increase in the rate of respiration, from 14 to 19 times a minute, which resulted in an increase in the minute volume of respiration of 3.2 liters. There were more significant changes in the function of the cardiovascular system. The venous pressure, which was normal (6.6 cm. of water) at the twelfth week of pregnancy, rose steadily to 16 cm. at the thirty-fourth week. It began to drop but rose again to 20.8 cm. in the fortieth week, at which time the patient complained of abdominal and chest pain. A fall in

Results of Tests for Objective Measurement of Respiratory and Cardiovascular Function

		Pulmonary Function							Cardiac Function		
						Maximum Breathing Capacity					
Date	Wk.	Tidal Volume, Cc.	Rate	Minute Volume, L.	Vital Capacity, Cc.	Depth, Cc.	× Rate =	M.B.C., L.	B.P., Mm.Hg	Venous Pressure, Cm. of Saline Solution	Increases in V.P. (Cm. Water) with 1,500 Cc. Saline Solution, I.V.
Prepneumonectomy	..	700	12	8.4	.....	1,450	28	40.6	100/60	4.0	6.0
Postpneumonectomy (1 yr.)	..	450	12	5.4	850	700	22	15.4	100/70	....	...
Pregnancy 7/6/48	12	610	15	9.2	1,050	600	32	19.2	100/68	6.6	6.4
8/9/48	17	450	14	6.3	1,160	786	22	17.3	116/80	....	...
9/7/48	21	550	14	7.7	1,050	800	28	22.4	100/60	....	...
10/5/48	25	600	16	9.6	950	500	30	15.0	100/72	....	...
10/26/48	28	550	17	9.3	1,000	600	28	16.8	110/70	15.5	4.5
11/16/48	30	600	17	10.2	1,000	700	28	19.6	130/70	....	...
12/10/48	34	...	..	....	.....	...	..	....	130/80	16.0	...
1/10/49	38	...	..	....	.....	...	..	....	120/80	13.0	...
1/13/49	39	500	19	9.5	1,000	650	34	22.1	120/70	9.8	6.0
1/22/49	40	600	17	10.2	1,050	700	32	22.4	120/80	20.8	7.0
1/27/49 Delivery	..	...	..	....	.....	...	..	....	136/80	11.8	...
									118/78	11.2	...
									98/60	7.4	...
1/28/49	..	650	13	8.5	1,100	950	22	20.9	112/70	10.2	...
1/31/49	..	...	..	....	.....	...	..	....	120/80	9.6	9.4
2/8/49	..	...	..	....	.....	...	..	....	100/60	11.6	7.2
4/4/49	..	650	14	9.1	1,100	900	24	21.6	103/65	18.6	5.0 *
10/24/49	..	350	12	4.2	1,040	500	36	18.0	112/70	14.0	...

* Patient had angina after intravenous injection of only 1,250 cc. of isotonic sodium chloride solution.

cubic centimeters. She was admitted to the hospital for study of pain in the right upper abdominal quadrant and thoracic discomfort on Jan. 10, 1949 but was discharged after three days when nothing abnormal was found.

Labor began spontaneously on January 27 and six hours after the onset the patient was delivered of a normal 8 pound (3,629 Gm.) female infant by low forceps while she was under tetracaine hydrochloride (pontocaine hydrochloride®) saddle block anesthesia. She lost approximately 700 cc. of blood from an atonic uterus. The postpartum course was afebrile and uneventful.

In addition to following the state of the patient by clinical signs and symptoms, we examined the patient at each antepartum visit by a series of tests designed to give some objective measurement of respiratory and cardiovascular function. The various parts of the ventilatory function (tidal volume, minute volume, vital capacity and maximum breathing capacity) were measured on a Roth-Benedict spirometer with the patient in the supine position after she had rested for an hour. The maximum breathing capacity was attained by voluntary effort, the patient being asked to breathe as deeply and as rapidly as possible for thirty seconds into the spirometer, from which the soda lime cannister had been removed. Venous pressure measurements were made with the patient in the supine position. While the patient was under local procaine anesthesia a 15 gage needle was placed in the antecubital vein and the pressure was measured in centimeters of water, the level of the right auricle pressure to 11.8 cm. occurred immediately before delivery, and it was at this same level immediately post partem; four hours later it was 7.4 cm., and on discharge from the hospital two weeks later it was again 11.6 cm. (5 cm. above the reading at the twelfth week of pregnancy). Seven weeks post partum it had risen to 18.6 cm. Seven months later it was 14.0 cm.

When the overload test was done early in pregnancy the result was abnormal. The rise in venous pressure was 6.4 cm. of water (normal, not more than 4 to 5 cm.). Although the initial venous pressure rose as pregnancy advanced, there was no other alteration of the response to overloading the circulation. In the fortieth week, the day after the patient received 1,500 cc. of isotonic sodium chloride solution intravenously, ankle edema developed for the first and only time. During the last test, seven weeks post partum, the patient experienced a cramping substernal pain and a sensation of dyspnea after 1,250 cc. of isotonic sodium chloride solution had been given intravenously. The electrocardiogram was unchanged from the previous record.

COMMENT

The ventilatory function prior to pneumonectomy was far from normal. The depth of respiration attained during maximum effort was 1,450 cc. (normal about 2,500 cc.), and the total

2. Lyons, R. H.; Kennedy, A. J., and Burwell, C. S.: The Measurement of Venous Pressure by the Direct Method, Am. Heart J. **16**: 675, 1938.

3. Caughey, J. L.: Effect of Rapid Infusion on Venous Presure: A Test of Cardiac Reserve, Proc. Soc. Exper. Biol. & Med. **32**: 973, 1935.

maximum breathing capacity was 40.6 liters (normal 85 or more liters). At this time there was no subjective complaint of dyspnea. Removal of the lung was followed by further reduction in ventilatory function, and, although compensatory adjustments permitted normal breathing at rest, disability was evident on effort, dyspnea resulting from moderate exertion. The depth of respiration attained on maximum effort was reduced 50 per cent to 600 to 800 cc. by pneumonectomy, but this was

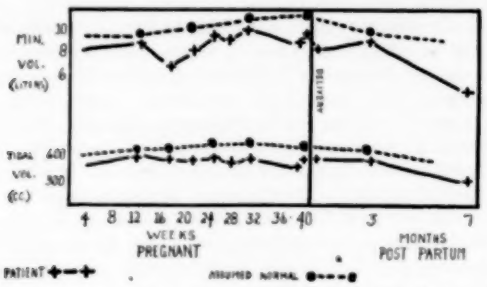

Fig. 1.—Changes in the patient's resting ventilation (tidal volume and minute volume) during and after pregnancy compared with the assumed normal changes.

compensated for by an increase in respiratory rate. The vital capacity was 850 cc. As a result of these changes the depth of respiration which could be attained on maximum effort was only slightly greater than the resting tidal volume. Thus, not only was there an extremely small respiratory reserve, but any increase in the volume of air moved could be accomplished only by an increase in respiratory rate, since little increase in the depth of respiration was possible.

In pregnant women with normal cardiovascular respiratory systems there is an increase in the minute volume of respiration due to an increase in the tidal volume.[4] In this patient there was no real increase in tidal volume and only a slight increase in the rate of respiration (fig. 1). No further decrease in vital capacity (fig. 2), depth of maximum breathing capacity (fig. 3) or respiratory reserve was observed. Although Thomson and Cohen[5] suggested that the vital capacity increases slightly as pregnancy advances and the subcostal angle widens, no such tendency was present in this case. Increased oxygen demand apparently was met by an increased efficiency in the absorption of oxygen, there being no real increase in the volume of air ventilated. As the pregnancy advanced the patient did notice increasing dyspnea on exertion, but this never became severe enough to be disabling.

A serious potentiality in this patient's case during the pregnancy lay in the fact that she had extremely low respiratory reserves. Had she experienced any further loss of lung volume from bronchopneumonia, atelectasis or infarction, she might have encountered serious difficulty, a true respiratory insufficiency. Fortunately, such complications did not occur.

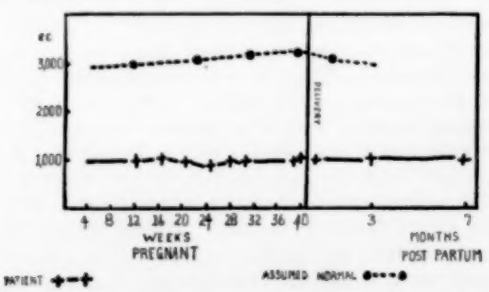

Fig. 2.—Changes in the patient's vital capacity during and after pregnancy compared with the assumed normal changes.

Although there were no clinical signs or symptoms of heart failure, certain abnormal objective changes occurred with respect to the cardiovascular system. The rise in peripheral venous pressure was not a normal response, for Thomson, Reid and Cohen[6] stated that the venous pressure tends to drop during pregnancy and to rise post partum. The pressure rose until the thirty-fourth week of pregnancy, then slowly fell (fig. 4). This rise and fall corresponds roughly to the reported increase and decrease in plasma volume which occurs during pregnancy.[7] During the fortieth week, the venous pressure rose to its highest point. The patient had no signs of heart failure. Whether or not the fact, as Caton[7] and associates have recently shown, that the extravascular fluid continues to increase through the last ten days of pregnancy had any bearing on this rise cannot be said. However, this increased extravascular fluid was probably the cause of the leg and ankle edema which followed the administration of 1,500 cc. of isotonic sodium chloride solution during the overload test in the fortieth week, the patient having had no edema at any other time during her pregnancy.

A more serious cardiovascular complication was an attack of angina during the overload test seven weeks post partum. So far the significance of this has not been determined. The electrocardiogram at this time showed no change from the antepartum record.

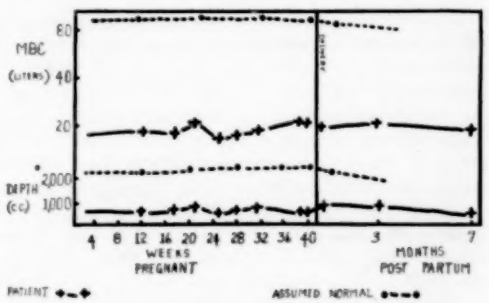

Fig. 3.—Changes in the patient's maximum breathing capacity (MBC) on voluntary effort compared with the assumed normal changes.

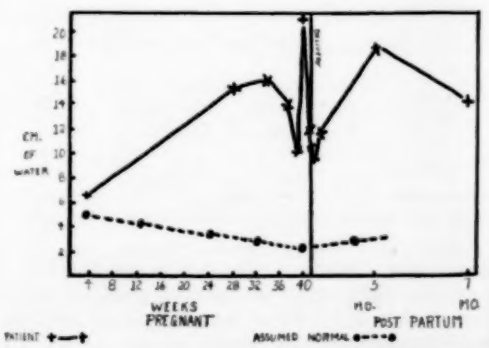

Fig. 4.—Changes in the patient's venous pressure during and after pregnancy compared with the assumed normal changes.

SUMMARY

1. A patient after a pneumonectomy with an extremely low respiratory reserve was able to complete a normal pregnancy and deliver uneventfully.

2. The load of pregnancy (i. e., increased oxygen requirements, increased blood volume and increased work of the heart) did not change the ventilatory portion of the respiratory function to any significant extent. Further decrease in functional lung tissue at any time during the pregnancy might have jeopardized both the life of the mother and that of the baby.

3. Changes occurred in the cardiovascular system, but their full significance is still unknown; the venous pressure rose and remained elevated post partum, and the patient had angina post partum on the performance of the overload test.

4. Plass, E. D., and Oberst, F. W.: Respiration and Pulmonary Ventilation in Normal Non-Pregnant, Pregnant and Puerperal Women, Am. J. Obst. & Gynec. **35**: 441, 1938.

5. Thomson, K. J., and Cohen, M. E.: Studies on the Circulation in Pregnancy: II. Vital Capacity Observations in Normal Pregnant Women, Surg., Gynec. & Obst. **66**: 591, 1938.

6. Thomson, K. J.; Reid, D. E., and Cohen, M. E.: Studies on the Circulation in Pregnancy: IV. Venous Pressure Observations in Normal Pregnant Women, in Pregnant Women with Compensated and Decompensated Heart Disease and in the Pregnancy "Toxemias," Am. J. M. Sc. **198**: 665, 1939.

7. Caton, W. B.; Roby, C. C.; Reid, D. E., and Gibson, J. G.: Plasma Volume and Extravascular Fluid Volume During Pregnancy and the Puerperium, Am. J. Obst. & Gynec. **57**: 471, 1949.

UNUSUAL REACTION TO PENICILLIN

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Severe transient allergic reactions to penicillin have been reported,[1] but to our knowledge no case of proved myocarditis and hepatitis associated with giant urticaria has ever been published. Watson [1b] reported a case in which there was severe indigestion, pain behind the sternum and swelling of the hands, feet and face, but he was unable to obtain any objective evidence of myocardial or hepatic derangement. The literature abounds with reports of structural and functional cardiac, renal and hepatic damage due to the so-called collagen diseases.[2] These changes are more or less permanent and are usually fatal. The allergic background for this condition has been stressed by Harris [2c] and Rich.[2d] On the other hand, Klemperer [3] hesitates to accept the doctrine of allergic origin for all the collagen diseases, especially lupus erythematosus. He points out that any number of chemical and physical agents may produce similar lesions.

Harkavy [4] prefers the term vascular allergy. He cites 3 cases of Shookoff and Lieberman as well as 1 of his own, with electrocardiographic evidence, to show the transient effect of acetylsalicylic acid and tobacco on the myocardium. Much more common than myocardial changes are arrhythmias due to allergens. Harkavy believes that these cardiovascular manifestations may be reversible in the early stages but later become irreversible because of chronic inflammatory and degenerative changes which may follow repeated single or multiple antigenic stimulation. He applies the term *formes frustes* of diffuse allergic vascular disease to cases in which recovery occurs.

REPORT OF CASE

The patient, a 53 year old white man, was given four intramuscular injections of procaine penicillin suspended in sesame oil daily. He was being treated for an external otitis. Ten days after the first injection he noted a rash of raised pink welts on his head, hands and feet and angioneurotic edema of the scrotum and penis. There had been no previous history of allergy or cardiovascular or hepatic disease. He had been treated with penicillin two years previously with no ill effects. The day prior to his first examination by us he had gone to a chiropodist because of extremely painful heels. He had been given a local injection of procaine hydrochloride without relief. He was first seen by us on the fourth day of his illness. The temperature was 98.8 F. and the blood pressure 112 systolic and 70 diastolic. There was a disseminated urticaria over the entire body and generalized lymphadenopathy. The heart and lungs were entirely normal. The abdomen was soft, and the liver and spleen were not palpable. He was given 2 mg. of epinephrine in peanut oil intramuscularly and 100 mg. of tripelennamine hydrochloride every four hours. On the following day the urticaria was worse. The blood pressure was 96 systolic and 70 diastolic and the temperature 98 F. Intravenous administration of calcium and intramuscular use of epinephrine were of no avail, and the patient was hospitalized. He was acutely ill, with edema of the mouth, tongue and pharynx. Dr. H. T. Behrmann described the skin lesions as giant urticaria. Diphenhydramine hydrochloride, 3 cc. every four hours intramuscularly, chloroprophenpyridamine maleate, 4 mg. every four hours, nicotinic acid, 50 to 100 mg. daily, and starch baths were given without success. Temperatures ranged as high as 103.4 F.

Laboratory examination of the blood showed: hemoglobin, 81 per cent (12.5 Gm. per hundred cubic centimeters); red blood cells, 4,260,000; white blood cells, 11,500, with 70 per cent polymorphonuclear forms, 17 per cent band cells, 8 per cent lymphocytes, 1 per cent eosinophils and 4 per cent monocytes. The white blood cell count rose to a high of 21,750, of which 96 per cent were polymorphonuclear cells and 75 per cent were young forms. Four days later the count was 9,600 white blood cells. The highest eosinophil count was 2 per cent. The urine was consistently normal. Blood culture was sterile. Additional tests showed: blood sugar, 103 mg., and urea nitrogen, 12.3 mg. per hundred cubic centimeters; cephalin flocculation reaction, 4 plus; thymol turbidity, 6.3 units; alkaline phosphatase, 13.2 Bodansky units; total protein, 4.63 Gm. (albumin, 2.28 Gm. and globulin, 2.35 Gm.), cholesterol, 249 mg., and cholesterol esters, 103 mg. per hundred cubic centimeters. Reaction to a precipitin test for Trichinella was positive, 1:1,280.

Repetition of tests of the liver function in three days showed a gradual improvement: cephalin flocculation reaction, 3 plus; thymol turbidity, 4.6 units; alkaline phosphatase, 8.1 Bodansky units, and cholesterol, 218 mg., and cholesterol esters, 127 mg. per hundred cubic centimeters.

Two weeks later the following results were obtained: cephalin flocculation reaction, negative; thymol turbidity, 3 units; alkaline phosphatase, 2 Bodansky units; cholesterol, 305 mg., and cholesterol esters, 249 mg. per hundred cubic centimeters, and total protein, 6.8 Gm. (albumin, 4.5 Gm. and globulin, 2.3 Gm.) per hundred cubic centimeters. A roentgenogram of the chest showed some calcified nodes but was otherwise normal.

The initial electrocardiogram was reported as showing myocardial involvement. The QRS group in leads 1, 2 and 3 was slurred; the T wave was low in lead 1 and inverted in leads 2 and 3, and the CF_1 lead had an upright T wave. One week later the T waves were upright in leads 2 and 3, and the T wave in lead CF_1 was diphasic.

The course of the disease was stormy. The edema of the tongue and pharynx was most alarming. There was never any jaundice. Itching was so intense that sleep was impossible until procaine hydrochloride was administered intravenously. Relief was dramatic. The hives disappeared. He was given 1 liter of 0.1 per cent procaine hydrochloride in 5 per cent dextrose solution and 500 cc. the next day. The duration of the dermatitis was thirteen days.

COMMENT

This case was reported because of the unusual complications of myocarditis and hepatitis. De la Vega and Mallen [5] could find no evidence of abnormal liver function or blood proteins in allergic persons. They concluded that liver dysfunction plays no role in the production of allergic disease, nor did they have any evidence to show that allergic phenomena may alter liver function. Hejtmancik and his associates [2a] reported 2 cases of allergic cardiovascular disease, 1 of which showed periarteritis nodosa of the periportal spaces, although liver function tests were normal. McCall and Pennock,[2b] in a review of cases of periarteritis nodosa, cite some cases of hepatic involvement with jaundice reported by Klotz, Kountz and Pass. We feel that the hepatic changes, as shown by results of liver function tests, were expressions of hepatocellular edema, which gave a laboratory picture of hepatitis without jaundice. The increased amount of alkaline phosphatase may have been due to periportal inflammation. No biopsy was made. The liver was never felt to be enlarged.

The myocardial changes are similar to those previously reported. These consist of inversion of the T waves and slurring of the QRS complexes. Complete reversion to a normal pattern points to a transient alteration in the conduction system of the myocardium. The basis for such change is either due to edema of the myocardium or anoxemia due to diminished coronary blood flow. In the absence of pain and a

1. (*a*) Walley, J. F. L.: Severe Reaction After Penicillin, Brit. M. J. **1**:150, 1948. (*b*) Watson, J.: Penicillin, Beeswax, and Allergy, Brit. M. J. **1**: 601, 1948.

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previous history of heart disease it seems most likely that the mechanism was one of inflammation of the myocardium.

A positive reaction to the precipitin test for Trichinella is often found in cases of periarteritis nodosa and other vascular allergies.[6] It is not specific for trichinosis. This patient had neither history nor typical laboratory findings for the diagnosis of Trichinella infection.

Another point of interest was the response to intravenously administered procaine hydrochloride. Although this medication was not given until the thirteenth day of illness, the relief was so dramatic that it seems most likely that the drug was of therapeutic benefit. In a self-limited condition it is difficult to evaluate any therapy, especially when administered so late in the course of the disease. Cohen and Kaufman[7] reported relief in 2 of 4 patients who had severe reactions to penicillin, and they felt that intravenously given procaine hydrochloride was worthy of further trial.

SUMMARY

1. A case of severe serum-like reaction to penicillin is reported.

2. Dermatitis, myocarditis, hepatitis and arthritis were the manifestations of this reaction. Electrocardiographic changes and altered hepatic function were observed.

3. Intravenously administered procaine hydrochloride seemed to be of therapeutic value.

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Council on Physical Medicine and Rehabilitation

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BASIC REQUIREMENTS IN SCHOOL LIGHTING

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Increased consideration has been given to school lighting during recent years. School committees, superintendents, medical men and architects are in need of a ready source of information concerning the basic requirements of illumination for school buildings. It is natural to turn to pamphlets on recommended or standard practice. The recommendations in these pamphlets should not be accepted uncritically. For instance, the minimum intensity recommended in 1948[1] for schoolrooms is 30 foot candles, although it was only 15 foot-candles in 1938.[2] It is pertinent to ask, Why the 100 per cent increase in a ten year period? Are people being educated to accept higher and higher illumination intensities? All will agree, of course, that there should be sufficient light for adequate seeing.

In prescribing illumination for any school, one should coordinate the intensity and distribution of light with the decoration, i. e., paint. The purpose of this paper is to examine critically the basic requirements in school lighting. Special attention will be given to the experimental backgrounds for the recommendations.

COLOR OF LIGHT

Several illuminants, varying in spectral character, are available for use.[3] Variation in the spectral character usually is accompanied with some changes in color of the light. In addition to daylight, the more common artificial illuminants are tungsten filament incandescent light, mercury arc light and fluorescent light. In ordinary seeing situations such as found in schools, efficiency of seeing is just as good under one as under any other of the illuminants.[4] But Holway and Jameson[5] claim that the quality of light derived from fluorescent lamps, no matter what combination of colors is used, is considered both unpleasant and distracting to workers in reading rooms. The quality is described as thin, harsh and cold. This psychologically undesirable quality of fluorescent light was not present in either daylight or in incandescent tungsten filament illumination. A recently devised fluorescent tube (soft white) appears to yield less disagreeable light.[6] Under the light of many of the fluorescent tubes, colors in decoration tend to go "flat" and the colors of objects are frequently altered in appearance. Thus the warmth and softness in colored paints are lost in comparison with the effect when incandescent light is used.

INTENSITY OF ILLUMINATION

Intensity of light adequate for effective and easy seeing is necessary in the school just as in any other situation where visual discrimination is required. Nevertheless, there is a difference between what is adequate and what is surplus light. Careful analysis of the experimental data employed as a basis for recommended intensities reveals in many instances either misinterpretation of data or invalid experimental procedures, for example, the experiment of Allphin,[7] which is frequently cited to support the view that greater light intensities influence school achievement. School progress was measured in November and in June in two classrooms, one with 4 to 6 foot-candles and the other with 20 foot-candles of light. In view of the results it was claimed that the children in the 20 foot-candle room gained 10 per cent more in educational age than those in the 4 to 6 foot-candle room. Tinker[8] points out a mistake in method of computing the percentages. Actually there was no appreciable difference in percentage gains in the two rooms. Another experiment cited in support of arguments for high intensities is the study by Luckiesh and Moss[9] on the relation between illumination intensity and nervous muscular tension resulting from visual effort. Measurements were made at 1, 10 and 100 foot-candles and the results presented in a logarithmic graph. This resulted in nearly a straight line graph. By replotting the data on a linear scale, Tinker[10] has shown that most of the decrease in muscular tension must have occurred at the lower intensities. There appeared to be only small

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10. Tinker, M. A.: Cautions Concerning Illumination Intensities Used for Reading, Am. J. Optometr. **12**: 43-51, 1935.

and insignificant changes from about 25 foot-candles to the higher levels. In the new Standard Practice for School Lighting,[1] a similar misinterpretation is made from Lythgoe's curve for visual acuity plotted on a logarithmic scale. All curves for gain in visual acuity with increase in illumination intensity flattened out at about 20 foot-candles. The gain is greatest up to about 10 foot-candles. It must be kept in mind, furthermore, that in measuring visual acuity, one is dealing with threshold values. It is highly questionable whether the almost microscopic gains in visual acuity obtained under the higher foot-candle levels justify their application to visual tasks where suprathreshold seeing is involved as in the schoolroom situation.

Data on visibility, measured by the Luckiesh-Moss visibility meter, are also cited to support the recommendations for high intensities.[1] Derived values (relative visibility) are cited, i. e., reading a newspaper text needs three times the foot-candles used to read 8 point Bodoni type in order that both be equally visible. Tinker [11] has questioned the validity of employing derived values for establishing adequate illumination intensities.

Preferences for light intensities have been used to support recommendations for high intensities for reading. Tinker's analysis [12] of the studies on preferences indicates that visual adaptation plays an important role in determining the preferences made under general illumination. In an experimental check, Tinker [12a] found that when readers were adapted to 8 foot-candles of light, the median choice for easy reading was 12 foot-candles. But when adapted to 52 foot-candles, the median choice was 52 foot-candles. Obviously, the intensity to which the reader is adapted largely determines his choice. In general the choices are centered about the intensity to which one is adapted. Use of light preferences for determining needed illumination intensity is a dubious practice.

A favorite criterion employed by Luckiesh [13] as a basis for prescribing (high) illumination intensities for visual work is frequency of blinking. Tinker's analysis [11] reveals a lack of validity for this technic as a criterion for specifying intensities of light needed for visual work. In an experimental check with an exact duplication of Luckiesh's technic, Tinker [14] found that rate of involuntary blinking did not reflect changes in ease of seeing and therefore is an invalid criterion.

In view of this analysis, it would seem that the high intensities recommended for adequate seeing,[11] such as 50 to 100 foot-candles for difficult reading, rest on a shaky experimental foundation. The materials in the pamphlets on recommended or standard practice should, therefore, be evaluated critically by those responsible for specifying school lighting. The ideal technic for determining needed illumination intensities probably would be to measure the relation of illumination levels to efficiency in terms of the physiologic cost of the work. As yet, no adequate technic for doing this has been devised. In the absence of such a technic it is necessary to make use of such measures as visual acuity, quickness of seeing and rate of work, which are all basically work output methods.

Analysis of the data on visual acuity in such standard works as Lythgoe [15] and Weston,[16] admitting that they are concerned with threshold values, reveals: gains in visual acuity can be obtained with intensities up to and beyond 1,000 foot-candles. The gains at the higher levels of intensity, however, are insignificant both in terms of practical amounts and statistical significance. Examination of the available data indicates that the major gains in visual acuity occur by the time 20 foot-candles is reached. For higher intensities, the curve of improvement flattens out rapidly. Beyond about 40 foot-candles it is practically horizontal. There are two important studies which reveal the statistical insignificance of gains at these higher levels of illumination. Simonson and Brozek [17] investigated the perceiving of very small capital letters (3.5 point) under 2, 5, 15, 50, 100 and 300 foot-candles of light. In this exacting visual work, there were no statistically significant changes in efficiency between 50 and 100 or 50 and 300 foot-candles. In fact, the slight increase from 15 to 50 foot-candles is apparently not significant. In the other study, by Kuntz and Sleight,[18] visual acuity was measured in relation to target brightness. Target brightness ranged from 3.16 to 1,000 foot-lamberts. A foot-lambert would be equivalent to a foot-candle if the reflection surface (i. e., page of book) reflected 100 per cent of incident light. Acuity of subjects with normal vision and with subnormal vision was measured. Employing an adequate standard of significance (at the 1 per cent confidence level), they found that with normal subjects there was no significant gain in acuity beyond 10 foot-lamberts; with the subnormal group, no significant gain beyond 31.6 foot-lamberts. Certainly if the slight gains at the higher intensities are not statistically significant, they cannot be significant in practical seeing situations. These last two studies furnish ample evidence that the minute gains in visual acuity obtained by adding excessive quantities of light are not significant when evaluated statistically and therefore have no value for practical application. The reader should be suspicious of any cited differences (gains) in experimental reports when statistical evaluation is not also given.

Critical levels of illumination have been determined for a number of seeing tasks.[3] The critical level of illumination is the intensity beyond which there is no further statistically significant increase in efficiency of performance as the foot-candles become greater. The following tabulation lists some of these critical illumination levels.

Reading legible print (10 pt)	3 to 4 f. c.
Reading and study of children	4 to 6 f. c.
Arithmetical computations	Less than 9.6 f. c.
Setting 6 point type by hand	20-22 f. c.
Threading a needle	30 f. c.
Reading newsprint[19]	7 f. c.
Recognizing letters in 3.5 point type[17]	Between 15 and 50 f. c.

Critical levels, of course, are not adequate levels of illumination. Tinker [20] has demonstrated this in a study

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13. Luckiesh, M.: Light, Vision and Seeing, New York, D. Van Nostrand Company, Inc., 1944.
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15. Lythgoe, R. J., and Corkhill, D. E.: The Measurement of Visual Acuity, Medical Research Council, Special Report Series, no. 173, London, His Majesty's Stationery Office, 1932.
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17. Simonson, E., and Brozek, J.: Effects of Illumination Level on Visual Performance and Fatigue, J. Optic Soc. America **38**: 384-397, 1948.
18. Kuntz, J. E., and Sleight, R. B.: Effect of Target Brightness on "Normal" and "Subnormal" Visual Acuity, J. Appl. Psychol., **33**: 83-91, 1949.
19. Tinker, M. A.: Illumination Intensities for Reading Newspaper Type, J. Educ. Psychol. **34**: 247-250, 1943.
20. Tinker, M. A.: Cumulative Effect of Marginal Conditions upon Rate of Perception in Reading, J. Appl. Psychol. **32**: 537, 1948.

on the cumulative effect of marginal conditions on rate of perception in reading. Furthermore, work output does not always indicate physiologic cost to the organism. How much illumination must be added to the critical level to provide a margin of safety is not certain at this time. By careful consideration, however, one can make an estimate. It would seem to me that the addition of 10 to 15 foot-candles to the critical levels should be adequate in ordinary seeing situations such as reading large book type (10 to 12 point). For the more exacting visual tasks perhaps one should add 20 to 25 foot-candles. There is no reason to conclude that more than 50 to 60 foot-candles are required for even the more exacting visual tasks of everyday life.

In regular classrooms, offices, study rooms, libraries and the like, an intensity anywhere between 20 and 30 foot-candles should be adequate. Where more exacting visual work is to be done, as in mechanical drawing and sewing, around 35 to 40 foot-candles will be found satisfactory. Darley and Ickis,[21] for instance, failed to demonstrate any statistically significant advantages from increasing the light intensity above 30 to 40 foot-candles in drafting rooms, and Holway and Jameson,[5] after extensive experiments, concluded that 20 foot-candles of light are needed on the work surface in offices and reading rooms. After an extensive survey of the literature, Carmichael and Dearborn [22] chose 16 foot-candles as adequate for reading in their experiments. In other parts of the school building less intensity is needed. Thus, about 15 to 20 foot-candles in gymnasiums and around 10 foot-candles in auditoriums and cafeterias will be satisfactory. Not less than 5 foot-candles should be used in halls and stairways.

DISTRIBUTION OF ILLUMINATION

A fundamental aspect of illumination, which is frequently inadequate in practice, is distribution of light and the brightness ratios of areas in the field of vision. Whenever light enters the eyes from any visible light source so that the effectiveness of vision is impaired or discomfort and annoyance is felt, or both things occur, glare is present. Brightness ratios refer to the brightness contrast that arises from variation in the brightness of adjoining areas within the field of vision.

Everyone is familiar with the disagreeable effects of a bright side light, or the reflection of light from a highly polished piece of metal, shining into the eyes while reading, while doing other visual work, or even when no exacting visual discrimination is involved. In addition to the discomfort felt, a glare source affects visibility of objects such as printed materials. The closer the glare source to the line of vision, the greater is the adverse effect on vision [4]; and the greater the number of glare sources in the field of vision, the greater the loss of visual efficiency. The use of adequate light fixtures properly arranged can eliminate most glare. In general, illumination should be as uniformly distributed as possible. All the light fixtures in the field of vision should have a surface brightness of not over 2 candles per square inch; 1 candle per square inch is better.

The relative brightness of adjoining areas in the visual field influences ease of seeing. For convenience the visual field may be divided into the central field, containing the visual task, and its immediate background, such as the pages of a book against which printed words are seen. The surrounds of the task extend out 30 degrees from the visual axis, and the peripheral field is beyond the surrounds just mentioned. A high brightness contrast between an object such as print and its immediate background is desirable for ease of seeing. When the surrounds as just defined are either brighter or darker than the central field, visibility of the objects to be discriminated tends to decrease.[4] For best vision the brightness ratios between the central field and the surrounds should not exceed 3 to 1. It is important that these ratios do not exceed 5 to 1, and in no circumstances should they be greater than 10 to 1.

The following points will aid in eliminating undesirable distribution of illumination and brightness in the school: 1. Avoid bright peripheral light sources, such as low-hanging fixtures that reach well down into the field of vision. 2. Avoid as far as possible the use of glazed paper, highly polished desk tops and other working surfaces. 3. Avoid any marked changes in brightness from one area to another in the field of vision. Thus desk tops should be of medium brightness, the wall around a blackboard should be fairly dark paint, and the strips of wall between windows and window frames should be light-colored paint. 4. Keep the surface brightness of light fixtures in the field of vision within the limits suggested herein. 5. Maintain, in general, as even a distribution of light as possible over work surfaces. Brightness ratios of adjoining areas should come within the limits suggested herein.

Intensity of light should be coordinated with control of glare and brightness ratios. In certain school situations, as in sewing rooms and shop work, an adequate intensity of light with satisfactory distribution is best obtained through a combination of general illumination of a moderate intensity and local lighting of the intensity needed for the discrimination required at the place of work. The ratio between local and general illumination intensity should be kept within the limits suggested for brightness ratios.

To achieve a pleasant environment and at the same time maintain good seeing conditions, it is necessary to coordinate lighting with decoration. This implies a control of the color and the reflection factor of paint and other surface finishes. In adequate lighting, much of the usable illumination comes from light reflected from the ceiling, walls and furnishings. The color scheme in the decoration should be pleasing. The reflection factors for various areas [1] should approximate the following specifications: ceiling and strip of wall near ceiling, 80 to 85; rest of walls, 50 to 60; wall space between windows including window frame, 75 to 85; doors, 30 to 40; desk and table tops, 35 to 50, and floors, 15 to 30 per cent. It should be added that there should be an area 24 to 30 inches wide of intermediate brightness surrounding dark blackboards, i. e., about 25 per cent reflection factor. This could well be a tack board.

SUMMARY

Schools should be illuminated so that effective and comfortable vision is possible. Furthermore the school environment should be pleasing. Intensity of light should be adequate for the various visual tasks. One cannot depend on the recommendations of intensities given in bulletins on standard practice. Controllable glare should be eliminated and brightness ratios within the visual field kept within satisfactory limits.

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22. Carmichael, L., and Dearborn, W. F.: Reading and Visual Fatigue, Boston, Houghton Mifflin Company, 1947.

Council on Foods and Nutrition

This paper was prepared at the request of the Council and is one of a series appearing in THE JOURNAL. *In the near future the entire series will appear in book form as the Council's Handbook of Nutrition.* JAMES R. WILSON, M.D., *Secretary.*

FLUID THERAPY

Relation to Tissue Composition and the Expenditure of Water and Electrolyte

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Probably the proper use of water and electrolyte solutions is responsible for saving more lives of seriously ill patients than is the use of any other group of substances. The beneficial effect may be direct, or the patients may be supported until the pathologic process can be corrected by specific measures or surgical intervention. Without a considerable knowledge of the physiology of body water and electrolytes, physicians cannot properly treat diseases accompanied by dehydration, edema, acidosis, alkalosis and shock or plan a rational therapy when fluids must be given parenterally or when electrolytes have been lost in sweat, urine and gastrointestinal secretions.

Previous concepts of the physiology of body fluids were dominated by two postulates which are now known to be erroneous. First, cellular membranes were regarded as practically impervious to sodium and potassium, and second, only alterations in extracellular fluids were thought to be readily accessible to fluid therapy. During the past fifteen years, analyses of tissue of experimental animals and determinations of balances of water and electrolytes in patients have demonstrated that intracellular fluids undergo fairly rapid changes in composition which alter profoundly the acid-base equilibrium of extracellular fluids. Furthermore, the changes in composition of intracellular fluid, particularly the loss of potassium, and the changes in electrolyte concentrations affect the function of cells. This new knowledge has provided a physiologic background which enables the physician to consider the composition of both extracellular and intracellular fluids in planning fluid therapy.

This paper will describe the chemical anatomy of both extracellular and intracellular fluids and will direct particular attention to the factors controlling the balance of sodium, potassium and chloride. These ions seem especially important since they seem to determine the content of water and the acid-base equilibrium of extracellular and intracellular compartments. The clinical significance of changes in the composition of body fluids will be pointed out. The final section will show how the new knowledge may be used to plan fluid therapy.

I. CONTROL OF VASCULAR AND EXTRACELLULAR COMPARTMENTS

The red cells and the plasma of the vascular compartment are about one fourth of the total extracellular constituents. The blood plasma may be considered the prototype of all extracellular fluids and, although the red cells must be considered intracellular, their function is intimately connected with that of the plasma. The movement of substances within the body and the exchange of water, solids and gases with the outside environment is accomplished by the rapidly moving constituents of the vascular compartment. Changes in body fluids are reflected in alterations in the volume and concentrations in the vascular compartment which provoke adjustments in the intake and the output by the kidneys as well as in the circulation and distribution of blood.

The movement of substances between the vascular and interstitial fluids is governed by a balanced exchange between the capillaries and interstitial spaces.[1] The movement of water and diffusible ions and molecules out of the capillaries is favored by the hydrostatic pressure within the capillaries and the colloid osmotic pressure of the perivascular fluids; the movement of these substances into the vascular compartment is favored by the colloid osmotic pressure of the plasma and the hydrostatic pressure of the perivascular fluids, which is exerted by the tissue tension. An example of this balanced mechanism is seen in the portal circulation, in which the low capillary pressure is balanced by a high colloid osmotic pressure of the perivascular fluid brought about by increased permeability of the liver capillaries to protein. Local changes in extracellular fluids are brought about by alterations in the capillary bed. Lymph channels provide an alternate route for the return of vascular fluid which is entering the interstitial spaces and are concerned particularly in the removal of protein.

Normally, the volume of the fluid of the vascular compartment is adjusted to the function of maintaining the exchange of metabolites in vital organs, first by redistributing the circulation according to the need but ultimately by altering the volume of plasma and extracellular fluids.[2]

The kidneys play the chief role in the control of the volume and concentrations of body fluids. However, the renal regulation is merely the crucial activity in a complex process integrated by the regulation of the cardiovascular system, the neurohypophysis, the humoral and neural control of the blood pressure and capillary bed and the adrenal and other endocrine glands. The control of the excretion of sodium and chloride determines the volume of extracellular fluids. According to present evidence, about 85 per cent of the glomerular filtrate is reabsorbed without changing the osmotic pressure of the tubular urine of the proximal tubules. Thus a large part of the reabsorption of water and sodium chloride is accomplished by processes that are intimately associated. The rate of this reabsorption can apparently be augmented in proportion to the load, which means according to the rate of glomerular filtration and plasma concentration. In the distal tubules sodium, bicarbonate and water are absorbed by processes which are more or less independent of each other and are under independent regulation. According to one theory,[3] the distal tubules tend to reabsorb sodium in quantities which, though known to be variable, tend to be relatively constant under some circumstances. If this is true, the excretion of sodium could be regulated in part by changes in the rate of glomerular filtration and the rate of reabsorption by the distal tubules. If glomerular filtration supplies an amount of sodium to the distal tubules which exceeds the rate of reabsorption, sodium will be excreted in the

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urine. On the other hand, if the rate of glomerular filtration is decreased and the distal tubular reabsorption remains the same, practically all the sodium which is filtered will be returned to the body. At a given extracellular volume, increase in the concentration of sodium in plasma augments the rate of glomerular filtration and tends to increase urinary excretion of sodium. The rate of water reabsorption in the distal tubules is under the control of the antidiuretic hormone of the hypophysis.[4] Increase in electrolyte concentration in extracellular fluids and diminution of body water leads to decrease in urinary volume through the activity of the antidiuretic hormone. Thus the theory is attractive because it provides a mechanism which can explain the regulation of both the volume and concentration of extracellular fluids. The weakness of the theory lies in the fact that the variations in the apparent rate of distal reabsorption of sodium are so great that experimental measurement of a constant rate cannot be substantiated because of inaccuracies in the methods and alterations produced by the observations themselves. It is known that the salt-retaining hormone of the adrenal cortex increases the rate of reabsorption of sodium, presumably in the distal tubules.[5] High venous pressure increases the rate of

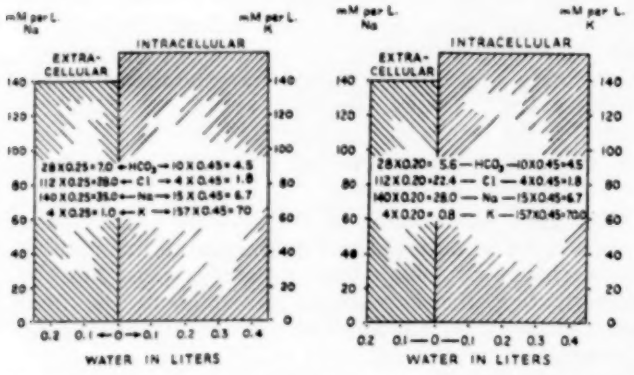

Fig. 1.—Diagrammatic representation of body water and electrolyte in 1 Kg. of tissue of a normal baby (left) and of a normal adult (right).

reabsorption of sodium in the absence of change in the rate of glomerular filtration.[6] Although cardiac failure is regularly accompanied by retention of sodium, decrease in the rate of glomerular filtration does not always occur. In any case, it is probable that diminution of the "functionally effective" volume of the vascular compartment provides the stimulus which provokes the renal response leading to retention of sodium and water such as follows the assumption of the erect posture, exercise, hemorrhage, shock, hypoproteinemic states and cardiac failure.[7] The mechanism by which this response is achieved is the subject of heated debate and arduous research. The following factors, individually or in any combination, may be involved: reduction in renal blood flow, reduction in the rate of glomerular filtration, increase in venous pressure, increase in the action of the hormone of the adrenal cortex on the kidneys and circulation and changes in blood pressure.

The regulation of body potassium through renal function is just beginning to receive the attention that it deserves. The kidneys can excrete more potassium than can be accounted for by the glomerular filtrate, and, though some potassium is always present in the urine, the concentration may be less than that of the plasma. It is not clear whether the salt-retaining hormone of the adrenal cortex increases the excretion of potassium by a direct effect on the renal tubules or whether potassium excretion is augmented indirectly when sodium excretion is decreased. High serum potassium concentrations increase urinary potassium; a rise in serum bicarbonate increases the urinary potassium. Many types of diuresis lead to losses of this ion.

The kidneys have the ability to control the acid-base equilibrium of the blood by regulating the acidity of the urine. This function demands adequate circulation and sufficient water and electrolyte. According to one theory,[8] an acid urine is produced by exchange of hydrogen ions for other cations. The same observations can be equally well explained by the effect of removal of carbonate and bicarbonate on the p_H of the remaining constituents of the glomerular filtrate.[9] The kidneys form ammonium, which may be substituted for other cations, and thereby save sodium and potassium, which would otherwise be necessary for the excretion of large amounts of anions. This mechanism takes twelve or more hours to come into full activity. The failure to reabsorb bicarbonate from the glomerular filtrate explains the excretion of an alkaline urine. It is noteworthy that formation of an alkaline urine fails to occur when there is a considerable deficit of electrolyte. The excretion of bicarbonate leads to loss of potassium in the urine, at least until there are considerable deficits of potassium in the body. It is also clear that deficits of potassium lead to losses of chloride until the deficits of both potassium and chloride are considerable. All the final regulations of the kidneys are inadequate when circulation is impaired or renal disease develops.

II. RELATION OF EXTRACELLULAR TO INTRACELLULAR WATER AND ELECTROLYTE

In order to enable the physician to visualize the quantitative relationships between extracellular and intracellular electrolyte, a schematic representation of the composition of the body has been presented.[10] The extracellular fluids are considered to have the composition of an ultrafiltrate of plasma. The intracellular concentrations are represented per kilogram of the intracellular water of rat and cat muscle. Data are available which indicate that the intracellular composition of muscle is approximately the same in young and mature cats and that human muscle has about the same composition as that of other mammals. Some of the changes in intracellular composition accompanying variations in extracellular composition are known not to be the same in other tissues, although similar changes are probably taking place. Since the intracellular fluid of muscle is about 70 per cent of the total intracellular fluid and has about the same composition as other intracellular fluids, the errors are not significant in depicting the relationship between extracellular and intracellular fluids for the body as a whole.

Figure 1 illustrates the relationships of extracellular and intracellular fluids of 1 Kg. of tissue in babies and adults. The extracellular concentration of sodium is represented on the ordinate for extracellular fluids, while the intracellular concentration of potassium is represented by the ordinate for intracellular fluids. The abscissas indicate the volumes of water in each instance. The amounts of sodium and potassium in the two phases are indicated by the respective areas. The amounts of the various electrolytes contained in each compartment are indicated by the concentrations multiplied by the volumes.

Total water is slightly greater per kilogram in infants than in adults. For the first months of life, extracel-

lular water of infants is about 30 per cent of the body weight. Although the intracellular water of adults is probably slightly less than 45 per cent of the body weight, this figure is suitable for all ages. Actually, the total body water varies appreciably in normal persons. The chief differences are accounted for by the fat content. Since fat is deposited with relatively little water, fat persons contain relatively less water per unit of weight. However, the quantitative relationships between the two types of fluid are essentially the same in normal persons except for the variations with age.

Since the changes in body water and acid-base equilibrium are explained chiefly by variations in water, sodium, potassium and chloride, the discussions will be limited chiefly to these constituents. First, total intracellular sodium is about 7 millimoles per kilogram, approximately equivalent to the extracellular bicarbonate and equal to one fifth to one fourth of total extracellular sodium. Normally, intracellular sodium is variable, since sodium can be transferred from intracellular to extracellular fluids and vice versa. The charts show the usual high normal value for intracellular sodium. Since the transfer is apparently accomplished without change in extracellular chloride, the effect on extracellular fluid is to alter the amount of sodium available to form bicarbonate. If total body electrolyte does not change, transfer of extracellular sodium to intracellular fluids decreases the concentration of bicarbonate in extracellular fluids, and transfer of intracellular sodium to extracellular fluids increases the concentration of bicarbonate in extracellular fluids. Hence, shift of sodium from extracellular to intracellular fluids and vice versa is an important mechanism for diminishing the variations in extracellular bicarbonate. In many clinical situations, this mechanism functions in addition to the usually described buffers of the blood.

Second, intracellular potassium in normal animals may be about 10 per cent lower than the values on the charts when there is no great disturbance in acid-base equilibrium or body water. The charts show the high normal value, since this is the one usually found in rats and cats. Changes in intracellular potassium may occur without detectable changes in intracellular sodium, though there is usually a reciprocal relationship between intracellular sodium and potassium.

Third, under abnormal conditions as much as one half of the intracellular potassium may be replaced by about two thirds of the equivalent amount of sodium. This change in intracellular electrolyte was first discovered in rats subjected to diets low in potassium [11] or receiving repeated injections of desoxycorticosterone acetate.[12] Conditions leading to losses of body potassium produce similar changes. Evidence of loss of intracellular potassium has been found as a result of maintenance of body fluids by continuous intravenous injection of solutions containing sodium chloride and dextrose,[13] as a result of diarrhea [14] and accompanying certain adrenocortical tumors causing Cushing's syndrome.[15] Under certain circumstances, alkalosis causes an increase in intracellular sodium and a decrease in intracellular potassium.[16] Acidosis is also accompanied by loss of intracellular potassium when there are deficiencies of water and other ions.[14] The changes in acid-base equilibrium which accompany the alterations in muscle sodium and potassium depend on the accompanying changes in body water, sodium, potassium and chloride.

Fourth, there is a predictable relationship between the acid-base equilibrium and the composition of muscle under certain circumstances.[17] Figure 2 shows this relationship between the concentration of bicarbonate in serum and the intracellular sodium and potassium of 157 Gm. of fat-free solids. Since this amount of fat-free solids is associated with 450 Gm. of intracellular water, the chart shows the intracellular composition for the same amount of intracellular water as figure 1 shows for 1 Kg. of tissue. The relationship was demonstrated for rats subjected to any one of the following conditions: (1) loss of chloride, or primary metabolic alkalosis; (2) loss of sodium, or primary metabolic acidosis, and (3) primary deficit of potassium. Since water and other ions were abundantly available, the relationship was demonstrated under conditions which permitted the kidneys to adjust body water and electrolyte when there was a deficit of one of the ions, sodium, potassium or chloride. The relationship may be regarded as a biologic equilibrium, or

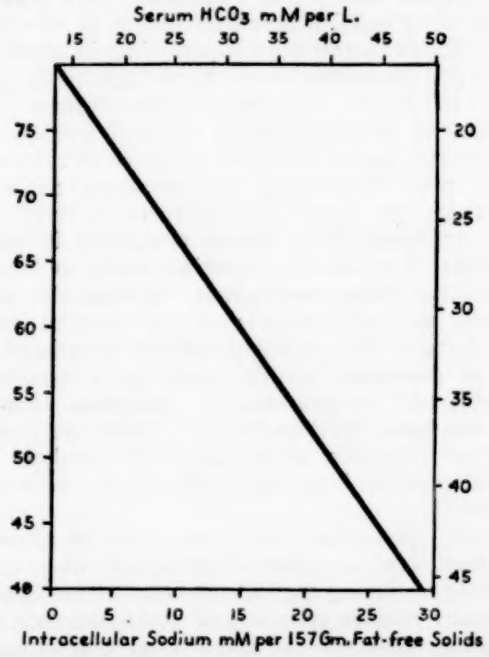

Fig 2.—The relationship of the concentration of bicarbonate in serum to the amount of sodium and potassium in the intracellular fluid of 1 Kg. of tissue. The left ordinate scale represents cell potassium, in millimoles per 157 Gm. fat-free solids. The right ordinate scale represents serum bicarbonate, in millimoles per liter. The diagonal line represents the relation of intracellular sodium to potassium. The bicarbonate values on the ordinate are the best fit for the potassium, while the bicarbonate values on the abscissa are the best fit for the intracellular sodium.

steady state, for these conditions. The equilibrium must be regarded as biologic since it is not attained for several days, and chemical equilibrium requires but several hours. The chart (fig. 2) is useful in illustrating the sort of changes which will tend to develop in the body with a deficit of one of these ions when the kidneys are able to maintain a relatively constant composition of the body fluids. The chart is based on data from rats, in which the relationship is readily demonstrated. Clinical studies indicate that the relationship is manifested in humans. In dogs [18] it is difficult to induce alkalosis in response to potassium deficiency, though the same changes in cell composition are readily attained.

It will be seen that deficit of chloride and deficit of potassium tend to produce the same changes in both extracellular and intracellular fluids. At biologic equilibrium, a deficit of one of these ions tends to lead to deficit of the other. Intracellular sodium may reach

levels several times the normal value and several times the equivalent of the bicarbonate in extracellular fluids. This relationship is important, first because alkalosis will tend to persist if potassium cannot be replaced and second because deficit of potassium will tend to lead to alkalosis if potassium is not restored. Acidosis not accompanied by loss of potassium, chloride or water leads to loss of intracellular sodium as well as relative deficit of extracellular sodium.[19] Thus, acidosis due solely to deficit of sodium would have an extracellular loss equal to the decrease in bicarbonate concentration multiplied by the volume of extracellular water, that is $(25 - 5) \times 0.25 = 5$ millimoles of sodium per kilogram of body weight, if the serum bicarbonate is 5 millimoles per liter. To this would be added the intracellular sodium (7 millimoles), making a total deficit of 12 millimoles per kilogram in a baby. Except as modified by changes in extracellular volume, the relative deficit of sodium in acidosis is unlikely to be greater than 12 millimoles per kilogram.

Of the three ions under discussion, only potassium seems to alter cellular functions owing to specific ion effects. High concentration of potassium in serum leads to prolonged conduction time, sharp, high T waves and, finally, heart block. The heart block develops at concentrations of 10 millimoles or more of potassium per liter of serum, but other minor evidence of cardiac disturbance may develop at concentrations as low as 7 millimoles per liter. Unless there is renal insufficiency or shock, high serum potassium is unlikely to develop. Low serum potassium leads to low voltages in the electrocardiogram, particularly of the T waves, and to paralysis of the skeletal muscle. These changes are probably always associated with deficit of potassium in the body as a whole. In rats subjected to pronounced potassium deficiency dilated intestines developed and no stools were passed. These rats may die as if they had paralytic ileus. The evidences of intestinal paralysis are relieved by potassium.[20]

Clinically, potassium deficit can only be proved by demonstration of a greater relative loss of potassium than nitrogen during the development of the condition or a greater relative retention of potassium than nitrogen during recovery. If body water and circulation are relatively normal, deficiency of potassium is likely to be accompanied by low concentration of potassium in serum. Under these conditions, certain patients show paralysis of the skeletal muscles and abnormal function of the cardiac muscles. Paralysis of skeletal muscles which is accompanied by low concentration of potassium in serum and relieved by administration of potassium salts was first recognized in familial periodic paralysis.[21] A similar disturbance has been described during the recovery from diabetic coma,[22] cholera [23] and sprue.[24] It probably occurs in infantile diarrhea and in certain cases of nephritis.[25] The effects of potassium deficiency on the heart are probably of great clinical significance. First, there is a functional disturbance leading to electrocardiographic changes, cardiac dilatation and failure. Later, actual necrosis of the myocardium develops.[26] Prevention and treatment of the disturbances in the heart will probably prove to be the chief advantages of the addition of potassium salts to the usual fluid therapy, but prevention of alkalosis and tetany may be important in some instances.

As will be discussed later, potassium deficiency develops because of an output greater than the intake as a result of diets low in potassium [22] or after prolonged maintenance of body fluids by infusions of dextrose and sodium chloride solutions.[13] Potassium deficiency may arise during normal intakes as a result of abnormal excretion in the urine in patients having certain adrenocortical tumors causing Cushing's syndrome [15] or in patients and animals receiving repeated injections of desoxycorticosterone acetate [26] and in certain cases of nephritis [25] and diabetes.[22] Increased losses of potassium in the stools occur in most cases of diarrhea.[14] Abnormal losses of potassium occur when intestinal secretions are lost through fistulas or suction drainage through catheters.[27]

The cells tend to lose potassium and gain sodium when the circulation is impaired in dehydration or shock or when there is tissue anoxia.[28] Possibly this transfer of potassium from the cells to the extracellular fluids and the accompanying urinary excretion is, in part, dependent on the increased activity of the adrenal cortex in response to "stress." [29] The release of potassium from the cells results in elevation of the concentration of this ion in the serum and increased excretion in the urine. As a result of alkalosis, a similar change in cellular composition takes place, accompanied by urinary loss of potassium.[17] It is not known whether the deficiency of potassium in alkalosis is initiated by the release of potassium from the cells or by altered renal function or both.

The disturbances in acid-base equilibrium have previously been described chiefly in terms of the relative contents of sodium and chloride in extracellular fluids. Since sodium shifts between extracellular and intracellular fluids, changes in acid-base equilibrium are now known to involve changes within the cells. The balances of potassium as well as those of sodium and chloride are involved in disturbances of the acid-base equilibrium.

The physicochemical factors controlling the acid-base equilibrium of the blood have been adequately discussed in a recent article by Singer and Hastings [30] as well as in textbooks.[31] The present discussion will, therefore, emphasize the relationship of the changes in the acid-base equilibrium of the blood to alterations in the composition of extracellular fluids and the accompanying changes in the cells.

Changes in the acid-base equilibrium may be defined as deviations from normal in the reaction or p_H of the blood. The p_H is determined by the ratio of the carbon dioxide to the bicarbonate of plasma. The concentration of carbon dioxide depends on the partial carbon dioxide pressure of arterial blood, which normally is equilibrated with the carbon dioxide of residual alveolar air. Hence, the carbon dioxide tension is subject to the regulation of pulmonary ventilation by the respiratory center. The concentration of bicarbonate in serum is dependent on the amount of base (cations) available to form bicarbonate at the particular carbon dioxide tension with the particular amounts of blood electrolyte. The base available to form bicarbonate is regulated by the kidneys. In as much as we are chiefly concerned with the content of water and electrolyte in body fluids, we shall neglect the relatively small changes in the buffering effect of the plasma proteins, red cells and phosphate and emphasize the content of the tissues in sodium, potassium and chloride. These ions are the chief factors determining the "base available to form bicarbonate." The cations available to form bicarbonate are the algebraic sum of total plasma cations minus the plasma anions, excluding bicarbonate, that is $(Na + K + Ca + Mg) - (Cl + HPO_4 + \text{proteins} + \text{sulfate} +$

lactate + keto acids —). For many purposes, the changes in base available to form bicarbonate in the body as a whole are adequately defined by balances of sodium plus potassium minus chloride.

Metabolic Acidosis.—Metabolic acidosis is produced by primary decrease in the concentration of cations available to form serum bicarbonate. It may be produced by relative increase in fixed acids or relative decrease in the concentration of total cations. An increase in the anions may arise as a result of ingestion of acidifying salts, through the endogenous production of organic acids owing to exercise, anoxia, hemorrhage, keto acids in starvation ketosis and diabetes or through the retention of phosphates and sulfates in renal insufficiency. A relative deficit of base may result from loss of intestinal or biliary secretions and through abnormal renal excretion.

The changes in intracellular electrolyte in metabolic acidosis are only beginning to be studied. Deficit of sodium alone, such as is illustrated in figure 2, is apparently relatively rare. If cation deficit is limited to sodium, the deficiency is measured by the decrease in concentration of bicarbonate in extracellular fluids plus the deficiency of sodium in intracellular fluids. The latter deficit is probably never greater than 7 millimoles per kilogram. Acidifying salts lead to retention of chloride without a corresponding retention of sodium. This type of acidosis is essentially like primary sodium deficit. The changes are illustrated by the effect of protein milk in babies,[19] and the probable intracellular composition is illustrated in figure 2.

Metabolic acidosis is usually accompanied by deficits of water, sodium, potassium and chloride. When there is acidosis and deficit of potassium, intracellular sodium apparently remains normal or may even be somewhat high, but it is not as high as when there is a similar deficit of potassium and no acidosis. The difference between the deficits of sodium and potassium and the deficit of chloride is a measure of the deficiency of cations causing acidosis. Since the deficit of sodium plus potassium may be greater than total normal extracellular bicarbonate plus normal intracellular sodium, most patients with acidosis cannot rationally be treated with sodium chloride and sodium bicarbonate alone. If intracellular potassium remains low, the amount of sodium in excess of chloride required to restore extracellular bicarbonate would be more than the normal total excess of sodium over chloride, including intracellular sodium. The changes in tissue composition indicate clearly that replacement of potassium as well as sodium and chloride is necessary in most cases of metabolic acidosis.

Metabolic Alkalosis.—Metabolic alkalosis is produced by primary increase in the sodium available to form bicarbonate in serum. Although metabolic alkalosis may be produced by relative excess of sodium, it usually results from relative deficit of chloride. The commonest cause is loss of gastric juice by vomiting or suction drainage. If sufficient water is available to permit renal adjustment, potassium will tend to be lost from the cells and sodium will partially replace the intracellular deficit of potassium. If the plan of therapy offers no opportunity for the body to replace the deficit of potassium, alkalosis may continue despite the administration of both sodium and chloride, because the biologic adjustment to the deficit of potassium leads to the maintenance of alkalosis by the kidneys. A similar reaction by the kidneys explains the development of alkalosis as a result of primary deficiency of potassium. In either case, recovery from alkalosis requires the replacement of potassium as well as chloride.

Respiratory Acidosis.—Respiratory acidosis results from primary increase in the carbon dioxide tension. Probably the most frequent cause is depression of pulmonary ventilation owing to narcosis, injury to the respiratory center or paralysis of the muscle of respiration. However, both acute and chronic respiratory acidosis may be produced by diseases of the lungs which lead to thickening of the alveolar walls, exudates, bronchiectasis and emphysema. Since oxygen diffuses less rapidly than carbon dioxide, the arterial blood becomes less saturated with oxygen than normal when carbon dioxide accumulates. Presumably, there is no change in body electrolyte in uncompensated respiratory acidosis.

Respiratory Alkalosis.—Respiratory alkalosis results from primary decrease in the carbon dioxide tension. It is produced by excessive pulmonary ventilation, such as occurs during exercise, fever or a disturbance in the respiratory center as a result of infections of the central nervous system, tumors and drugs (salicylates). Overventilation may occur in hysterical patients or as a result of anoxia in cardiac failure or at high altitudes. Uncompensated respiratory alkalosis presumably results in no change in body electrolyte.

The disturbances in acid-base equilibrium have been discussed as if only the carbon dioxide tension or the cations available to form bicarbonate were altered. Actually, the alteration of one of these variables leads to compensatory variation in the others. In metabolic acidosis, the respiratory center responds so as to increase the pulmonary ventilation and reduce the carbon dioxide tension. The reduction is not sufficient to lead to a normal p_H of the blood. In metabolic alkalosis, the respiratory center may reduce pulmonary ventilation, but the reaction is limited because anoxia tends to be produced.

On the other hand, the kidneys may alter the cations available to form bicarbonate in both respiratory acidosis and alkalosis. In respiratory alkalosis, the serum bicarbonate may be reduced fairly rapidly, but as long as the disturbance in respiration persists the blood p_H remains normal or slightly alkaline. However, after the kidneys have produced the reduction in available cations, the respiratory center may recover and respond normally. The patient will then have true metabolic acidosis. Since recovery from the effects of drugs such as salicylates may be rather rapid, respiratory alkalosis is likely to go through a phase of metabolic acidosis during recovery.

In respiratory acidosis, the kidneys may increase the cations available to form bicarbonate to high levels (45 millimoles per liter of serum). The blood p_H remains more acid than normal, and arterial blood shows a diminution of oxygen saturation. In respiratory acidosis due to lung disease, there is unlikely to be a sufficiently rapid recovery of lung function to produce a true metabolic alkalosis during recovery.

It is not known whether compensated respiratory alkalosis and acidosis produce changes in cell sodium and potassium. It is likely that such is the case and that compensated respiratory alkalosis leads to diminution of cell sodium and compensated respiratory acidosis leads to increase in cell sodium and decrease in cell potassium.

Disturbances in body water and electrolyte involve changes in the volume and electrolyte concentration which are just as important as the changes in acid-base equilibrium. Dehydration usually involves a decrease in electrolyte as well as water. If the loss of electrolyte is proportionately greater than the loss of water, there is a decrease in the concentration of electrolyte in serum. This type of change may be called hypotonic dehydration. Darrow and Yannet [32] produced loss of extracellular electrolyte without change in body water. The concentration of sodium and chloride decreased in the serum, while the concentration of serum proteins and hemoglobin increased. The animals looked sick, refused food and were weak. The volume of urine decreased; the rate of glomerular filtration decreased, and the nonprotein nitrogen rose. The cardiac output was strikingly decreased.[33] It could be shown that the volume of extracellular water decreased, while the volume of intracellular water increased. The clinical picture was essentially the same as it is in the usual dehydration seen in patients. The experiments are important because they emphasize that the central feature of hypotonic dehydration is loss of extracellular electrolyte.

For practical purposes, hypotonic dehydration may be considered to result from loss of proportionately more electrolyte than water, although rare cases may involve little or no deficit of water. With low concentration of serum electrolyte, the cells contain more water than normal. Statistically, the increase in cell water in experiments producing deficit of extracellular electrolyte is only about two-thirds as much as would reduce the electrolyte concentration of the intracellular fluids of muscle as much as the reduction of extracellular concentration.[34] In chronic states of this sort, the relationship may be somewhat different. In any case, the disturbances in circulation, renal function and muscular strength are dependent not only on the decrease in extracellular water and plasma but also on decrease in electrolyte concentration.[35] Hypotonic dehydration produces the picture called medical shock and responds to replacement of electrolyte, but the response is somewhat better when blood or plasma as well as electrolyte are given.[36]

Hypertonic dehydration results when the loss of water is proportionately greater than the loss of electrolyte. This leads to increase in the concentration of electrolyte in serum.[37] It can be shown that relatively pure increase in extracellular electrolyte leads to increase in extracellular water and dehydration of the cells.[32] Patients with hypertonic dehydration may show symptoms of shock, but circulatory failure is less prominent than in hypotonic dehydration. Patients and experimental animals with hypertonic serums show evidence of cerebral damage; death is likely to be accompanied by high temperature and respiratory paralysis.

Edema is due to increase in the volume of extracellular water. While the changes in composition of the intracellular fluids are not known, it is usually assumed that cellular structure is well preserved. However, there is no reason to doubt that the cells undergo the same sort of changes in composition when the concentrations and acid-base equilibrium of the serum are altered as has been shown to be the case when there is no increase in extracellular volume. Thus, hypotonic edema should produce increased hydration of the cells, while hypertonic edema should lead to dehydration of the cells. There is evidence that low electrolyte concentration in patients with edema leads to circulatory failure similar to that seen in hypotonic dehydration. Renal function and circulation may be improved by raising the electrolyte concentration by giving sodium chloride and sodium bicarbonate. Although hypertonic edema occurs, increase in the concentration of extracellular electrolyte in patients with edema usually leads to further expansion of extracellular fluids. It is likely that some patients with edema show the changes in cellular composition illustrated in figure 2 when there is change in serum bicarbonate concentration due to relative deficit of one ion.

With these general comments as a background, the changes in tissue composition in certain diseases will be discussed briefly. Infantile diarrhea produces deficits of water, sodium, potassium and chloride. Considerable variation in the absolute and relative losses of these constituents is shown. The serums may be hypotonic or hypertonic. Metabolic acidosis is usually present in severe cases. The balances during recovery in 8 severe cases showed an average deficit per kilogram of body weight of 125 ml. of water, 9.2 millimoles of chloride, 9.5 millimoles of sodium and 10 millimoles of potassium.[38] Since the deficiency of sodium for the body as a whole is equivalent to the deficiency of chloride, the acidosis is largely explained by transfer of extracellular sodium to the cells. This conclusion is evident from the fact that the low concentration of bicarbonate indicates relative deficiency of sodium in extracellular fluids. The deficiency of potassium is equivalent to about one seventh of the total estimated intracellular potassium content or about one-fourth the equivalent of the total extracellular sodium. The abnormally high intracellular sodium is not as great as the deficit of potassium would predict in figure 2. The deficit of potassium is sufficient to explain the development of acidosis with no deficit of sodium in relation to chloride. The acidosis in infantile diarrhea is, therefore, dependent on deficit of potassium occurring in patients with a deficiency of water, sodium and chloride.

Figure 3 illustrates the probable state of body fluids in the dehydration of infantile diarrhea. The deficit of extracellular water and electrolyte is about one fourth of the normal content. If infants with diarrhea are treated with sodium chloride and water alone, the deficit of potassium persists and sodium enters the cells because of the deficit of potassium.[38] If sufficient water is available for renal adjustment, high intracellular sodium and low intracellular potassium will result. This will lead to high concentration of bicarbonate and low concentration of potassium in serum. Alkalosis probably also aggravates the tendency toward development of low serum calcium.[39] All these disturbances will disappear when food, with its high content of potassium, can be absorbed. Indeed the success of treatment with solutions containing sodium chloride and sodium bicarbonate is dependent on sufficiently rapid recovery to permit feeding.

If sodium chloride is given with insufficient water to permit renal adjustment, acidosis may persist or be aggravated. Case 3 of a previous study [38] illustrates this course of events. The patient had severe diarrhea and was treated with the addition of small amounts of sodium chloride to a milk mixture which gave too little water for a patient with diarrhea. On admission, the concentrations of bicarbonate and chloride were, respectively, 7 and 123 millimoles per liter. During recovery practically no change in body sodium or chloride occurred, but 13 millimoles of potassium and 100 Gm. of water per kilogram of body weight were

retained. Since the diarrhea would have led to deficits of sodium and chloride if salt had not been given, the addition of sodium chloride to the food had prevented deficits of these ions from developing before the admission to the hospital and before the study was started. The acidosis had probably been aggravated by transfer of sodium to the cells, since sufficient water was not available to permit renal adjustment. The persistent deficit of potassium explains the transfer of sodium to the cells. On entry the patient had deficit of water and potassium leading to acidosis and hypertonic dehydration. The picture was the result of treatment of diarrhea with sodium chloride and insufficient water.

Adults with diarrhea have not been studied with methods which demonstrate the actual deficits of water and electrolyte. Nevertheless, it has long been known that adults lose large amounts of water, sodium, potassium and chloride in dysentery and cholera.[40] Paralysis of skeletal muscles has been recognized following treatment of cholera,[23] and these paralyses were relieved by injections of potassium chloride. Similar observations have been made in sprue.[24] There can be little doubt that diarrhea in adults leads to striking deficits of potassium as well as sodium and chloride and that these losses are similar to those in infantile diarrhea.

About twenty years ago, Atchley and others [41] showed that diabetic acidosis is associated with losses of potassium as well as sodium and chloride. Holler [22] and others [42] recognized paralysis during recovery which was accompanied by low concentration of potassium in serum and was relieved by potassium salts. We found that the retentions during recovery in 1 case of severe diabetic acidosis in an 8 year old girl were 100 Gm. of water, 8 millimoles of chloride, 12 millimoles of sodium and 6 millimoles of potassium per kilogram of body weight. The serum concentrations of phosphorus decrease somewhat more strikingly during recovery from diabetic acidosis than do those of infants recovering from diarrhea. The changes in body electrolyte in diabetic acidosis apparently resemble those of infantile diarrhea, and the mechanism of hypokaliemia is dependent chiefly on depletion of intracellular potassium while the patient is becoming acidotic.[42a]

The acidosis of renal failure has not been studied adequately from the point of view of changes in both extracellular and intracellular composition. Patients with nephritis may show low concentrations of bicarbonate, chloride and sodium, but the intracellular changes accompanying these alterations are not known.[43] The usual explanation of the electrolyte changes is failure of the kidneys to form a concentrated urine, which conserves sodium chloride and preserves the acid-base balance. The inability to form an acid urine which contains ammonium is the chief explanation of the acidosis. The inability to excrete phosphate aggravates this disturbance. Certain patients with chronic nephritis have shown weakness and paralysis which is relieved by administration of potassium salts. These patients have low concentrations of potassium in the serum [25] and presumably in the muscles.[44] The logical explanation is that the kidneys are unable to conserve potassium. This observation suggests that deficit of potassium may aggravate acidosis through the transfer of extracellular sodium to the cells in patients who have a deficit of sodium chloride and tend to lose potassium. However, when there is oliguria, the concentration of potassium in serum may rise to levels associated with heart block.[45] Indeed, potassium intoxication is one of the events leading to death in experimental anuria [45a,b] and in some cases of uremia.[45c]

All the symptoms of loss of extracellular water and electrolyte may be produced by immobilization of water and electrolytes at the site of an exudate or tissue injury. Burns and crushing injuries to muscles are examples of disturbances of this type.[46] It has been shown that the fluids which accumulate at the site of injury contain all the essential elements of extracellular fluids and plasma. Although the fluids are not lost from the body as a whole, the water and electrolytes are not available to the rest of the tissues. Thus, it is not surprising that traumatic shock with immobilization of extracellular water and electrolyte and medical shock due to loss of extracellular electrolytes show the same clinical phenomena of peripheral circulatory collapse, oliguria and anoxia of the tissues.

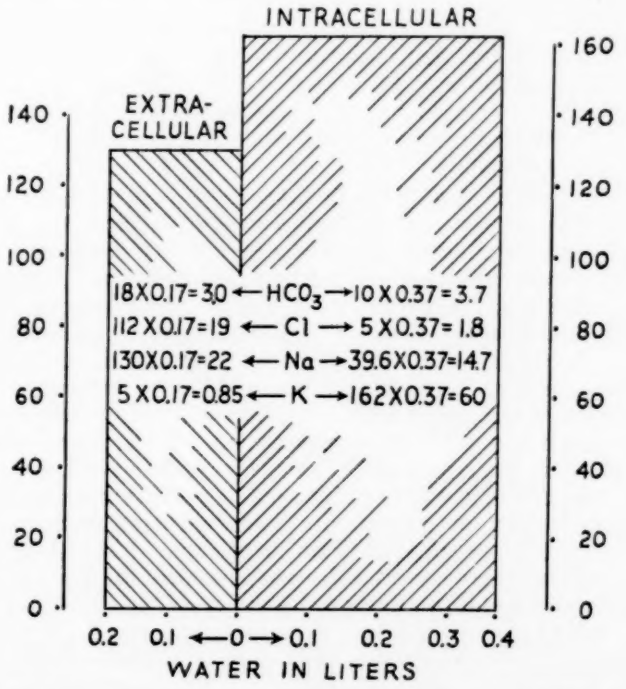

Fig. 3.—Diagrammatic representation of body water and electrolyte in 1 Kg. of tissue of a baby with dehydration resulting from diarrhea. The left ordinate scale represents sodium and the right ordinate scale potassium, both in millimoles per liter.

When the circulation is interrupted or impaired by shock or exposure to cold,[47] the intracellular fluids of the muscles lose potassium and gain sodium. As was pointed out earlier, transfer of extracellular sodium to the cells produces metabolic acidosis when there is failure of renal adjustment of body electrolyte. The cellular loss of potassium raises the concentration of potassium in serum. If renal function is adequate, the potassium will be excreted in the urine. A similar exchange of potassium for sodium in the cells occurs in anoxia and explains the rise in concentration of potassium in serum in peripheral vascular failure. High concentrations of serum potassium are frequently found in diarrhea and diabetic coma before treatment is initiated, despite the fact that the intracellular fluids are deficient in this ion. This sort of reaction leading to urinary excretion of potassium explains in part the loss of this ion in diarrhea, diabetic acidosis and other conditions. However, the chief interest is the fact that

internal shifts of sodium as well as loss of sodium from the body act together to produce acidosis.

Alkalosis is usually the result of primary deficit of chloride produced by vomiting. We have determined the retentions during recovery in 2 patients with congenital pyloric obstruction. In both patients there was evidence of abnormally high intracellular sodium before treatment. One patient retained a moderate amount of potassium during recovery, while the other did not. Presumably, some patients with alkalosis due to primary deficit of chloride will get enough potassium from food to prevent loss of potassium, but others will show deficiency of potassium as well as greater deficit of chloride than sodium.[48] It should be remembered that the presence of high intracellular sodium in alkalosis indicates that the relative excess of sodium over chloride in the body as a whole is much greater than the excess in extracellular fluids as revealed by the serum concentrations of sodium and chloride. The large amount of intracellular sodium explains the slow response of some patients to administration of sodium chloride. The fact that the potassium deficit persists means that, in accordance with the relationship depicted in figure 2, the kidneys will not excrete sodium so as to decrease the bicarbonate in the serum until potassium is available.

Prolonged duodenal drainage after operative procedures provides the conditions for development of alkalosis with potassium deficiency. The removal of the gastric fluid depletes the body of more chloride than sodium and produces alkalosis. The administration of sodium chloride facilitates the excretion of potassium by the kidneys. While sodium chloride is usually administered in sufficient amounts to replace extracellular electrolyte, the development of potassium deficiency alters the renal function so that metabolic alkalosis persists. The alkalosis probably develops because of a chloride deficit, but it persists because of a deficiency of potassium. These patients have low concentrations of potassium in serum. Clinical and chemical improvement follows replacement of potassium as well as sodium chloride.[49]

McQuarrie and others [15a] called attention to certain patients with Cushing's syndrome who have alkalosis refractory to administration of sodium chloride but responding to potassium salts. The serums show not only high concentrations of bicarbonate but low chloride and potassium. Kepler and others [50] studied a patient who recovered from alkalosis after removal of an adrenocortical tumor but in whom alkalosis again developed when metastases became manifest. Analyses of the muscle of these patients would probably show low potassium and high sodium. The patients suffer from primary deficit of potassium produced by certain adrenocortical steroids which increase the excretion of potassium by the kidneys. The same picture can be produced by repeated injections of desoxycorticosterone acetate [17] or, less readily, by diets low in potassium. The experimental animals receiving desoxycorticosterone acetate show high intracellular sodium and low potassium in muscle together with definite alkalosis of the serum.

Edema represents chiefly an expansion of the extracellular water and electrolyte. The mechanisms promoting the formation of edema which act locally in the exchange of fluid between the capillaries and interstitial fluids are: increased hydrostatic pressure in heart failure and venous obstruction; decrease in the serum concentration of albumin in nutritional edema, nephrosis, nephritis and liver diseases; the presence of interstitial proteins in abnormal amounts in allergic reactions, myxedema and acute nephritis, and decreased absorption of fluids by the lymphatics in some diseases. Ultimately, the volume and concentration of body fluids is controlled by the kidneys.

III. EXPENDITURE OF WATER AND ELECTROLYTE

Since the maintenance of body water and electrolyte demands that the intake equal the output, the factors controlling the expenditure of water and electrolyte must be understood by physicians. The important pathways of losses of water and electrolyte are (1) the lungs and skin, (2) the urine and (3) the gastrointestinal tract. The loss from the lungs and skin may be divided into the insensible losses occurring when there is no sweat and those involving activity of sweat glands. The insensible water loss, excluding sweat, is roughly correlated with heat production, so that 42 Gm. are lost for each 100 calories produced.[51] Insensible water loss is accompanied with negligible losses of electrolyte.

The substances presented to the kidneys for excretion are chiefly the end products of protein metabolism together with other osmotically active substances, of which electrolytes are the most important. Renal load is proportional to the metabolic mixture being burned in the body. Although different diets may contain different amounts of protein and electrolytes, the ordinary mixed diets of patients are sufficiently alike to permit an approximate estimation of the renal load from the calories. During fasting, the renal load consists largely of the end product of protein metabolism together with electrolytes freed by the breakdown of the tissues. The metabolic mixture during fasting probably varies somewhat with age and nutritional status. When all other food is omitted, administration of dextrose reduces the renal load not only to the extent that protein is spared but also by abolishing ketosis, which requires excretion of these acids together with electrolyte.[52] Minimal protein metabolism is attained by administration of 4 to 5 Gm. of carbohydrate per 100 calories metabolized. During fasting, the renal load depends on caloric production, except that the load is diminished by administration of dextrose. The concentration of the urine determines the volume of water excreted by the kidneys and is dependent on the renal load, the water intake and the ability of the kidneys to form either a concentrated or dilute urine. The amount of urinary water which contains a given load varies inversely with the urinary concentration.[52b]

Stool water is dependent chiefly on the residue of the diet, which, in general, is proportional to the caloric intake. During fasting, stool water is negligible unless there is diarrhea. Normal stool water is about 4 Gm. per 100 calories of diet and is such a small part of the total water expenditure that it is negligible for most purposes.

Figure 4 shows the urinary volume per 100 calories on the ordinate and the urinary concentrations on the abscissa. The area labeled "diet" gives the urinary volumes with the usual adult diet. The area marked "dextrose" gives the urinary volumes during omission of all food except enough dextrose to produce maximal reduction of renal load. Complete fasting requires intermediate volumes. Artificially fed infants fall in

the lower part of the area marked "diet." Because of the low content of protein and electrolyte in human milk, the renal load of the breast-fed infant is almost as low as that indicated by the dextrose area.

The total water requirement is calculated as in the following manner: 1. The caloric production is estimated from the age, weight, activity and food intake. 2. The area appropriate for the diet, fasting or dextrose feeding, is chosen. 3. From the chart, the urinary volume per 100 calories is obtained for an appropriate urinary concentration—usually at a specific gravity of 1.012. 4. This volume is multiplied by one hundredth of the estimated caloric production to obtain the urinary volume. 5. For each 100 calories metabolized, 42 ml. of water are required to cover the insensible water loss. The sum of the urinary volume and the insensible water loss gives the water expenditure, excluding sweat, stool water and abnormal losses. Since complete absence of sweat is unlikely, 15 to 20 ml. per 100 calories metabolized should be added to cover total water expenditure in the absence of abnormal losses or large volumes of sweat.

For the normal person who is without sweat and on a normal diet and who has a urinary specific gravity of 1.012, the previous calculations indicate that water expenditure is 126 ml. per 100 calories, or 140 ml., assigning a small allowance for sweat and stool water. Since babies metabolize about 100 calories per kilogram, this figure gives the water requirement of infants per kilogram of body weight. An adult metabolizing 3,000 calories would require 3,800 to 4,200 ml., or 54 to 60 ml. per kilogram if the metabolism is 43 calories per kilogram. If the values are calculated for a urinary specific gravity of 1.024, a baby would require 88 ml. per kilogram of body weight if there is no sweating. An adult would require 2,650 ml., or 38 ml. per kilogram of body weight. These figures are minimal, except as modified by reduced caloric production or diets giving low renal loads. In calculating the water intake it should be kept in mind that the water available for expenditure is equal to the water intake plus the water of oxidation. The water of oxidation is about 12 ml. per 100 calories metabolized of the usual metabolic mixture. During fasting a small amount of water is made available for expenditure by decrease in tissue water.

The usually prescribed intake of infants is 150 ml. per kilogram, which would lead to a urinary specific gravity of about 1.008 if there were no sweating or abnormal losses. A similar intake per 100 calories metabolized in an adult would be 4,500 ml. At this level of intake, the kidneys could, if so required, save about 62 ml. of water per 100 calories metabolized, or a total of 1,860 ml. for the average adult. This level of intake may be necessary for most infants, since they cannot readily make known their need for water. Adults will voluntarily regulate their intake so as to lead to a moderately concentrated urine. It may be advisable to prescribe as high an intake as this for children and adults if sweating or abnormal losses are likely to occur.

Unless there is considerable sweating or abnormal loss, the intake of electrolyte with the diet or that freed from breakdown of tissues during fasting is sufficient to replace the losses through skin, stools and urine. The urine can be rendered practically free of sodium and chloride. Data on the ability of the kidneys to conserve potassium are meager, but it appears that the normal kidney can produce urine which contains potassium at no greater concentration than that of the serum. Therefore, the minimal urinary losses of electrolytes are 0.2 millimoles of chloride and sodium and 0.4 millimoles of potassium per 100 calories metabolized. The minimal daily losses in 1 year old infants are about 2 millimoles of sodium chloride and 4 millimoles of potassium. Corresponding adult losses would be about fourfold. When food is taken, stool losses are about 0.1 millimoles of sodium chloride and 0.4 millimoles of potassium per 100 calories. Stool electrolyte is negligible during fasting unless there is diarrhea.

Metabolic studies indicate that the insensible water loss is slightly greater than can be accounted for by caloric production under ordinary circumstances in infants,[53] children [54] and adults.[51] This observation indicates that a moderate amount of sweat is usually being formed. An average estimate is 10 ml. of water, 0.5 millimoles of sodium and chloride and 0.2 millimoles of potassium per 100 calories metabolized. The average sweat losses in adults would be 300 ml. of water, 15 millimoles of sodium and chloride and 6 millimoles of potassium.

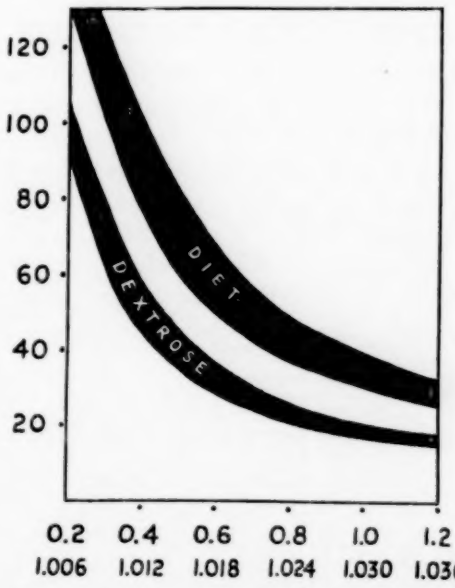

Fig. 4.—The urinary volume required to excrete the solids presented to the kidneys for excretion by the metabolism of 100 calories. The ordinate scale represents milliliters of water per hundred calories; the upper abscissa scale represents osmoles per liter, and the lower, specific gravity.

Allowances for growth are of little practical significance inasmuch as the usual diets provide abundant water and electrolyte. The daily retentions during the first year of life are 10 ml. of water, 0.6 millimoles of sodium, 0.4 millimoles of chloride and 1.5 millimoles of potassium. During periods of rapid growth, the retentions may be twice these values, and from the third to the tenth year they may be about half as great.

In summary, the water requirements can be predicted fairly confidently for normal conditions by the calculations described in the discussion of figure 4. The minimal losses of electrolyte in a 1 year old infant are probably about 8 millimoles each of chloride, sodium and potassium, or about 0.5 Gm. of sodium chloride and 0.33 Gm. of potassium. The average minimal losses of an adult would be 2.5 Gm. of sodium chloride and 1.5 Gm. of potassium. Probably, somewhat larger amounts should be given, since minimal expenditure cannot be anticipated.

(To Be Continued)

THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION

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SATURDAY, MAY 27, 1950

UNITED STATES PHARMACOPEIA

One of the most important decennial meetings of the United States Pharmacopeial Convention was the recent meeting in Washington, D. C. Preceding the convention was a conference, at which time a series of simultaneous meetings was held on scientific subjects of pharmacopeial interest. These included reviews of the status of pharmacopeial standards for protein hydrolysates, antibiotics, water for pharmaceutic uses, volatile oils, vegetable drugs and dermatologic preparations and other topics.

The convention considered and adopted with some modification the recommendations of the Committee on Constitution and By-Laws, which was appointed at the 1940 convention meeting. This committee reported at a special meeting in 1942, at which time the proposed by-laws were adopted, but the constitution was held over until the 1950 meeting. The changes in the constitution were extensive but reflected the attempts of those who are interested in the United States Pharmacopeia to insure continued progress of this organization.

At this convention officers and members of the Committee of Revision for the 1950-1960 convention were elected. The president is Dr. Allen H. Bunce of Georgia. Dr. Bunce, who had been chairman of the Committee on Constitution and By-Laws, succeeded Dr. Carey Eggleston. Adley B. Nichols and W. Paul Briggs were reelected secretary and treasurer, respectively. The vice president is Dr. Theodore G. Klumpp. The Board of Trustees, which includes two representatives from medicine, two from pharmacy and two at large, consists of Robert L. Swain, editor, *Drug Topics* and *Drug Trade News*; P. H. Costello, secretary, National Association of Boards of Pharmacy; Ernest Little of the College of Pharmacy, Rutgers University; Carson P. Frailey, executive vice president, American Drug Manufacturers Association; Arthur C. DeGraff, professor of therapeutics, New York University College of Medicine, and Austin Smith, editor of THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION. Swain, Costello and Little were members of the preceding Board of Trustees; the others are newly elected. Lloyd C. Miller was introduced as the director of the Committee of Revision for 1950-1960. He succeeded Dr. E. Fullerton Cook, who for five decades has worked closely with the United States Pharmacopeia. Dr. Cook gave untiring service during his time as director of the Committee of Revision and was eulogized on several occasions at the convention.

The United States Pharmacopeia is an official compendium under the provisions of the Federal Food, Drug and Cosmetic Act and is of outstanding importance in the establishment of drug standards for the enforcement of this act. Thus it has tremendous influence in industrial and other circles and is of great importance in the protection of the health of the people. Furthermore, it is internationally known and has been officially recognized in a number of Latin American countries. Those who have an opportunity to serve the Pharmacopeia and its interests have a right to cherish this opportunity. Because of the nature of the Pharmacopeia and what it represents, those who are responsible for its affairs cannot think of personal interest; they must always have in mind the interest of the Pharmacopeia. The newly elected officers and members of the Committee of Revision for the 1950-1960 United States Pharmacopeial Convention should have the continued support of medical, pharmacal and allied organizations in their work.

RETROLENTAL FIBROPLASIA

Terry [1] in 1941 observed a fibroplastic overgrowth of persistent vascular sheath behind each crystalline lens in the eyes of a prematurely born infant. In 1945 there were some 162 cases observed in the United States. The syndrome, which Terry [2] characterized as retrolental fibroplasia, includes the following features: an opaque vascularized membrane behind the lens, microphthalmia, shallow anterior chamber, fetal blue iris, thin ciliary processes in front of the opaque tissue, searching nystagmus, apparent photophobia, persistent hyaloid artery and often retinal separation. A similar condition has been observed rarely in full term infants at birth, and always unilaterally.

The pathogenesis of the syndrome appeared to be based on three conditions: (1) persistence of some part of the tunica vasculosa lentis system, (2) a growth of embryonic tissue behind the crystalline lens and (3) persistence of the fibrillar structures of the vitreous humor.

1. Terry, T. L.: Extreme Prematurity and Fibroblastic Overgrowth of Persistent Vascular Sheath Behind Each Crystalline Lens, Am. J. Ophth. **25**: 203 (Feb.) 1942.

2. Terry, T. L.: Ocular Maldevelopment in Extremely Premature Infants: Retrolental Fibroplasia; VI. General Consideration, J. A. M. A. **128**: 582 (June 23) 1945.

The predisposing cause of this bilateral development appeared to be, in the opinion of Terry, premature birth in the stage early enough for the hyaloid artery with its tunica vasculosa lentis and pupillary membrane to be patent. The condition develops largely, if not entirely, after birth. The abnormality was observed in infants 4 to 6 months of age. Separation of the retina was probably caused by traction of persistent strands of fibrillar vitreous which adhere firmly to the retina. Terry speculated that precocious increase in blood pressure brought on before the hyaloid artery and the tunica vasculosa lentis disappear constitutes the principal factor. After the development of increased blood pressure, hypertrophy of the hyaloid arterial system takes place, causing persistence of fibrillar vitreous and growth of a support of embryonic connective tissue.

The hyaloid vascular system ceases to carry blood eight and a half months after conception, and infants born earlier than this have a functioning hyaloid vascular system. In this meshwork the embryonic connective tissue can develop, thus producing retrolental fibroplasia.

Krause [3] in 1946 reported 18 similar cases, which, however, he considered to be instances of congenital encephalo-ophthalmic dysplasia affecting the neuroectoderm primarily and associated structures secondarily at an early age. On the basis of 50 cases and 17 autopsies, Reese and Payne [4] state that the basic lesion in this condition is a persistence in part or in toto of the primary vitreous with or without hyperplasia and with or without secondary changes consequent to hemorrhage, opening of the lens capsule and glaucoma. Twenty per cent of their patients had skin hemangiomas at birth.

Owens and Owens [5] were first to study the development of the lesion. They studied the progress of the disease in the eyes of 25 infants. In every case the eyes showed no abnormality at birth. The Owenses emphasized particularly that all remnants of the hyaloid artery had disappeared before the onset of the early stage of the disease. The earliest abnormality in their cases was dilatation of the retinal vessels followed by extensive retinal edema. The arteries became tortuous; the retinal vessels became partly buried in masses of swollen retina. As the disease progressed, the vitreous became hazy and the swollen retina raised. In most cases the peripheral folds of retina fused behind the lens to form a complete membrane. The Owenses concluded that the disease was not of congenital origin and that it was not related to the persistence of the hyaloid artery.

3. Krause, A. C.: Congenital Encephalo-Ophthalmic Dysplasia, Arch. Ophth. **36**: 387 (Oct.) 1946.
4. Reese, A. B., and Payne, F.: Persistence and Hyperplasia of the Primary Vitreous (Tunica Vasculosa Lentis or Retrolental Fibroplasia), Am. J. Ophth. **29**: 1 (Jan.) 1946.
5. Owens, W. C., and Owens, E. U.: Retrolental Fibroplasia in Premature Infants, Tr. Am. Acad. Ophth. **53**: 18 (Sept.-Oct.) 1948.

In a recent issue of the *Archives of Ophthalmology* King [6] presented data on 238 patients with retrolental fibroplasia. This series includes Terry's original 117 patients and 121 additional patients. King points out that the incidence of retrolental fibroplasia varies for different localities and for different hospitals in the same locality. Investigations into the causative factors of the condition were largely without positive results. There was no evidence of a hereditary factor, nor were any social factors apparently responsible. One hundred and seventy-seven of the patients in this series were born eight to 18 weeks prematurely. The cause of prematurity was often obscure. Maternal disease during pregnancy had no bearing on the occurrence of retrolental fibroplasia in the offspring. The Rh factor was not of any significance. Rubella occurred in only 1 case. Of all the possible causes considered, exposure to light is the most tenable factor.

The diagnosis of the condition is usually not difficult. The two conditions that have to be differentiated from it are retinoblastoma and pseudoglioma. The condition is, as a rule, bilateral, with the following signs: (1) lack of differentiation of the iris, (2) shallow or flat anterior chamber, (3) posterior synechias, (4) membrane behind the lens, (5) elongated processes of the ciliary body, (6) vessels radiating over the surface of the membrane from a central point and (7) retinal detachments. Congenital anomalies were not strikingly evident in this series. The only one to occur in significant numbers was cutaneous hemangioma of the skin at birth. Krause, Kinsey and Zacharias reported the incidence of hemangiomas in premature infants with retrolental fibroplasia to be 14 per cent but pointed out that the incidence for premature babies without infected eyes was 15 per cent. In King's series, hemangiomas of the skin were present in 40 patients (17.5 per cent). Synechias were the commonest complication in this group. Glaucoma is another important complication. It was detected in 43, or 16 per cent, of the patients in King's series. Terry emphasized the importance of retinal complications such as retinal separation, retinal folds or a healed lesion of chorioretinitis.

Children with retrolental fibroplasia display the behavior patterns common to blind children. Prematurely born children in general are slower in developing than full term children. Children with retrolental fibroplasia do not show any higher incidence of retardation than the average group of premature children.

The prognosis in retrolental fibroplasia is unfavorable, and both medical and surgical therapy are of little value. The infant should be kept in a dark room. Mydriatics and miotics are used to prevent the complication of posterior synechia and glaucoma. Over 10 per cent of the infants born prematurely, weighing 3 pounds

6. King, M. J.: Retrolental Fibroplasia: A Clinical Study of 238 Cases, Arch. Ophth. **43**: 694 (April) 1950.

(1,361 Gm.) or less, can be expected to be blind from retrolental fibroplasia, according to Terry. If this percentage remains, at least 600 cases will occur annually, thus increasing the blind census materially.

The disease is sufficiently frequent and severe to merit attention to prevention. In the absence of knowledge of the causation of the condition, prophylactic measures should be directed toward prevention of prematurity.

Current Comment

REGISTRATION UNDER THE HARRISON NARCOTIC ACT

Physicians who are registered under the Harrison Narcotic Act or under the Marihuana Tax Act must effect reregistration on or before July 1 to avoid a penalty. Each year, despite the annual warnings in THE JOURNAL, this requirement is overlooked by some physicians and unpleasant consequences follow. Failure to register adds a penalty of 25 per cent to the tax payable and, in addition, subjects the physician to the possibility of a fine not exceeding $2,000 or to imprisonment for not exceeding five years, or to both. As an act of grace the Commissioner of Internal Revenue has in the past years given some tardy registrants the choice between paying sums by way of compromise, a procedure authorized by law, or accepting criminal prosecution. If this procedure does not produce the required promptness in reregistration, the commissioner will have no choice but to institute criminal prosecution.

SYPHILITIC OPTIC ATROPHY

Klauder and Meyer [1] call attention to recent histologic studies which demonstrate that syphilitic optic atrophy occurs in two forms: (1) an inflammatory form with secondary degeneration of the nerve fibers and (2) a primary degeneration in the form of tabetic atrophy of the nerve. Bruetsch [2] observed, by staining alternating serial sections of optic pathways with toluidine blue and with Weil's myelin sheath stain, simultaneous existence of both the inflammatory and degenerative phase of syphilitic optic nerve atrophy. He emphasized that the degenerative changes in optic atrophy are preceded by an inflammatory exudative phase. Visual field defects may be caused by the exudative processes in the marginal zone before atrophy of the nerve fibers has taken place, and such defects may improve or disappear after antisyphilitic treatment. Klauder and Meyer stress the necessity of an early ophthalmologic diagnosis, on the basis of a study of 397 patients with syphilitic primary optic nerve. Among the earliest symptoms of syphilitic optic nerve they list loss of dark adaptation, visual field defect, loss of field for color and pallor of the optic disk. They stress the necessity of an early ophthalmologic and perimetric examination of all patients with neurosyphilis regardless of whether the serologic reactions of the blood and spinal fluid are positive or negative. The presence of pupillary abnormalities calls for examination of the cerebrospinal fluid in order to exclude optic nerve atrophy. Treatment in the preatrophic stage in the cases reported by them prevented progress of the disease and preserved the visual acuity. It appears, therefore, that the problem of syphilitic optic nerve atrophy as a cause of blindness is concerned principally with early diagnosis. The ophthalmoscope and perimeter, according to these authors, are as essential as the spinal puncture needle in the diagnosis and management of syphilis and its complication, primary optic nerve atrophy.

1. Klauder, J. V., and Meyer, G. P.: Early Diagnosis of Syphilitic Primary Optic Nerve Atrophy, Arch. Ophth. **43**: 537 (March) 1950.
2. Bruetsch, W. L.: The Frequency of Syphilitic Primary Optic Atrophy in Dementia Paralytica: A Clinico Anatomic Study, Am. J. Psychiat. **104**: 725 (May) 1948.

RESPONSE TO SURVEY OF PHYSICIANS' INCOMES

The first report on the number of returns in the survey of physicians' incomes indicates that more than 37,000 replies have been received by the U. S. Department of Commerce to the 100,000 short form (white) questionnaires mailed out by the Department of Commerce several weeks ago. More than 50,000 returns are desired before June 15. Physicians who have not returned their white questionnaires, especially young physicians and others whose practices are not extensive, should do so soon. Another group of questionnaires is now being mailed to 25,000 physicians who did not receive white questionnaires. This group will be identified by the code number of the Bureau of Medical Economic Research on the returned franked envelope. The purpose of the identifying number is to enable the Bureau of Medical Economic Research to address follow-up questionnaires to physicians who do not reply to the first mailing. In fact, two follow-ups, if necessary, will be sent, in the hope of getting from 20,000 to 24,000 replies. Of this group, 10,000 will receive the short form (buff in color) schedules; 15,000 will receive the long form (green), which covers 1945 to 1948 as well as 1949. Some physicians have objected to question 9 (which is number 8 on the green copies) because the physician is required to record the name of his town, which, along with his specialty, seems to be a violation of the secrecy of the return. Only the size of the town is actually needed. The Department of Commerce insists that requesting the name of the town is the only accurate way to get the correct population size. It should be understood that a survey of physicians' incomes would have been made by the United States Department of Commerce alone if this joint survey had not been conducted.

WASHINGTON NEWS

Compulsory Health Insurance

Although national compulsory health insurance is a dead issue for this session of Congress, all indications in Washington are that it will not stay dead for long. In the coming campaigns, both the AFL and CIO are expected to make good use of a new pamphlet produced by the Democratic National Committee to promote the Truman Health Plan. The title is "Better Medical Care That You Can Afford." It is expertly prepared for mass appeal. By oversimplifying the issues, it runs through the whole complicated subject of national health and national health insurance in about five minutes' reading time. In several places the pamphlet has condensed some significant facts right out of its pages. For example, it states that under the Truman Plan, "you would choose your own doctor," and "the doctor would choose his patients," with no reference to the fact that in many cases practical considerations would make this choice one of theory only. It also makes the flat statement that costs of operating voluntary plans "are higher than national health insurance," ignoring the fact that any costs under a national health insurance plan are, at this stage, merely an estimate. Furthermore, the pamphlet says that "a worker would pay one and one half per cent of earnings under $400 per month," without noting that this is merely a rough guess at its cost and that any deficit would have to come out of the United States Treasury. Whatever its factual errors, and whatever the explanation for them, "Better Medical Care That You Can Afford" appears to be a sharp, effective piece of propaganda.

Medical Reserves

News of importance to medical reserves of the Army, Navy and Air Force is developing in official announcements. The first came from the Army, which said that all reserve officers expecting to take summer field training would be required to have their immunization inoculations brought up to date. The Navy and Air Force also are drafting similar regulations but so far have not made public announcements. For some months officials have been discussing a plan requiring all reserves to bring their medical records up to date with inoculations and booster injections. However, this was deferred for obvious reasons. If that decision is reversed later, it would mean a major medical program. The reserves total almost 600,000 men, and 335,000 are enrolled in the National Guard, for which reinoculation also probably would be required. The Army is requiring men going on summer training to be immunized against smallpox, typhoid, paratyphoid and tetanus. If the men have records of original immunization, the Army says that only a "stimulating" dose of typhoid-paratyphoid vaccine and tetanus toxoid need be administered.

For the present this applies only to men planning to go on active duty this summer, for periods of 14 days or more. A total of 26,431 medical officers are enrolled in the military reserves, but the Defense Department had no figures on the number scheduled for summer active duty tours.

Incidentally, the role of the reserves is not lessened under the new draft bill, although they may not be called up until Congress gives its approval. The House Armed Services Committee, in amending the bill, stated that the reserves must be the immediate back-stoppers to the regular forces in an emergency. They may be called into active duty as soon as Congress declares such an emergency. "The ordering into service of reservists should precede, not follow, the resorting to inductions of draftees," the Committee report said. "This, in the Committee's view, is exceedingly important."

Veterans Economy Cuts

The Veterans Administration medical department, while saved from two recent drastic economy cuts, still has financial worries. A VA request for $2,191,000 to keep its medical staff intact this year is before the House Appropriations Committee, with approval of the Budget Bureau. It is not having so much success in getting through Congress another request for $20,000,000 (also for this year) to cover pay increases, mostly in the medical department. In a third appeal, VA is trying for Budget Bureau approval of an additional $23,000,000, which would be added to next year's budget. Without these three special funds, a total of $45,191,000, VA maintains it cannot get through the next twelve months. VA medical department has another minor worry; it cannot determine what the House meant by "medical" personnel when it exempted them from a 10 per cent payroll slash. Must cooks, bakers and laundry personnel be laid off? If so, some VA officials point out that the "medical" staffs' efficiency will be cut down. The Senate, which has still to act on the House payroll cuts, might settle this question for VA.

World Health Organization

This country technically is in arrears in its payment for support of the World Health Organization, whose assembly is meeting now in Geneva. When Congress approved membership in WHO, it set a ceiling of $1,920,000 on our annual appropriation. Last year WHO established a budget of seven million dollars for the calendar year 1950, which would call for a United States contribution of $2,500,000, or something like half a million in excess of our legal ceiling. At the time WHO explained that, although the United States would be expected to contribute more dollars, its percentage of the total WHO budget was being reduced from 38.4 to 36.

To allow for this added amount, legislation was introduced to increase our authorized contribution. Congress deferred action on this request, but it did approve another $1,920,000 contribution. The result is that currently the United States is running behind the budget established by WHO, although it is paid up to the last penny on what our own law allows.

Government officials closely connected with WHO are not optimistic that the ceiling will be lifted at this session. The difficulty is that this legislation (H. J. Res. 334) would also increase United States contributions to a number of other international organizations. Unfortunately for WHO, one of these organizations is the International Labor Organization. Because ILO, whether accurately or not, is subject to criticism as a "red-dominated organization," the administration is reluctant to bring the bill out of the Rules Committee and onto the floor of the House, so the prospect is that WHO will have to make out with the lesser amount, at least until the next session of Congress. Next year, prospects are that the same situation will continue—the United States paying what Congress has agreed to, but not what WHO wants. Last week the WHO finance committee reduced the United States contribution for 1951 from 36 to 35 per cent. This means a reduction of $71,000 in the amount WHO believes the United States should pay. However, the total United States contribution, according to the WHO budget, would still be almost $2,500,000, or about half a million more than Congress indicates it is willing to spend.

Other FTC Actions

In another action, FTC reports a stipulation agreement with International Laboratories, Inc., of Rochester, N. Y. The company has agreed to stop representing that its product, Moone's Emerald Oil, has any therapeutic value in treatment of a variety of skin irritations ". . . beyond relieving or alleviating the symptom of itching." In a second stipulation, Benson Laboratories, Inc., agreed to stop representing that Formula A-N-1, a medicinal preparation, prevents or cures colds or is effective for relief of minor throat irritations due to colds. The company also agreed to cease making other advertising claims. The Commission says both stipulations were approved ". . . in accordance with the Commission's policy of encouraging law observance through cooperation in certain types of cases where there has been no intent to defraud or mislead." This remedy was reported on by the Council on Pharmacy and Chemistry and the Council on Industrial Health in THE JOURNAL (131: 1421 [Aug. 24] 1946).

ORGANIZATION SECTION

Official Notes

TELEVISION

The television at the annual session of the American Medical Association in San Francisco will be provided through the courtesy of Smith, Kline and French Laboratories and will be broadcast from the Veterans Administration Hospital, Fort Miley, 42d Avenue and Clement Street, San Francisco, to the Masonic Temple, where visitors to the Annual Session may view it. The television program was published in THE JOURNAL May 20 (page 257).

REVISED EDITION OF MOTION PICTURE REVIEWS NOW AVAILABLE

The Committee on Medical Motion Pictures has completed the second revised edition of the booklet entitled "Reviews of Medical Motion Pictures." This booklet now contains 225 reviews of medical and health films reviewed in THE JOURNAL to Jan. 1, 1950. Each film has been indexed according to subject matter. The purpose of these reviews is to provide a brief description and an evaluation of motion pictures which are available to the medical profession. Each film is reviewed by competent authorities. Copies are available at 25 cents each from the Order Department, American Medical Association, 535 North Dearborn Street, Chicago 10.

Coming Medical Meetings

American Medical Association, San Francisco, June 26-30. Dr. George F. Lull, 535 North Dearborn St., Chicago 10, Secretary.

Aero Medical Association, Chicago, May 29-31. Dr. Thomas H. Sutherland, 214 S. State St., Marion, Ohio, Secretary.

American Association for the Surgery of Trauma, Salt Lake City, June 22-24. Dr. Charles G. Johnston, 1512 St. Antoine St., Detroit 26, Secretary.

American College of Chest Physicians, San Francisco, June 22-25. Mr. Murray Kornfeld, 500 N. Dearborn St., Chicago 10, Executive Secretary.

American College of Radiology, San Francisco, June 25. Mr. William C. Stronach, 20 N. Wacker Drive, Chicago 6, Executive Secretary.

American Dermatological Association, Jasper National Park, Alberta, Canada, June 18-22. Dr. Louis A. Brunsting, 102 Second Ave. S.W., Rochester, Minn., Secretary.

American Diabetes Association, San Francisco, Hotel Whitcomb, June 24-25. Dr. John A. Reed, 1 Nevins St., Brooklyn 17, Secretary.

American Geriatrics Society, New York, Hotel Commodore, June 1-3. Dr. Malford W. Thewlis, 25 Mechanic St., Wakefield, R. I., Secretary.

American Hearing Society, Chicago, Drake Hotel, June 15-17. Mrs. Frances E. Lee, 817 Fourteenth St., N.W., Washington 5, D. C., Secretary.

American Heart Association, San Francisco, Fairmont Hotel, June 22-25. Dr. John J. Sampson, 1775 Broadway, New York 19, Secretary.

American Medical Women's Association, Carmel, Calif., June 20-22. Dr. Grace Talbott, 909 Hyde St., San Francisco 9, Secretary.

American Neurological Association, Atlantic City, Claridge Hotel, June 12-14. Dr. H. Houston Merritt, 710 W. 168th St., New York 32, Secretary.

American Ophthalmological Society, Hot Springs, Va., The Homestead, May 31-June 2. Dr. Maynard C. Wheeler, 30 W. 59th St., New York 19, Secretary.

American Proctologic Society, Los Angeles, July 1-5. Dr. W. Wendell Green, 1838 Parkwood Ave., Toledo 2, Ohio, Secretary.

American Society for the Study of Sterility, San Francisco, Sir Francis Drake Hotel, June 24-25. Dr. John O. Haman, 490 Post St., San Francisco 2, Secretary.

American Society of X-Ray Technicians, Columbus, Ohio, Deschler-Wallick Hotel, May 28-June 2. Genevieve J. Eilert, R.T., 16 Fourteenth St., Fond du Lac, Wis., Executive Secretary.

American Urological Association, Washington, D. C., Hotel Statler, May 29-June 1. Dr. Charles H. deT. Shivers, Boardwalk National Arcade Bldg., Atlantic City, N. J., Secretary.

Association for the Study of Internal Secretions, San Francisco, June 23-24. Dr. Henry H. Turner, 1200 N. Walker St., Oklahoma City 3, Secretary.

Conference of Presidents and Other Officers of State Medical Associations, San Francisco, Palace Hotel, June 25. Mr. John E. Farrell, 106 Francis St., Providence, R. I., Secretary.

Maine Medical Association, Poland Spring, June 18-20. Dr. Frederick R. Carter, 142 High St., Portland 3, Secretary.

Medical Library Association, Boston, June 19-22. Miss Helen Hlavac, 209 East 23d St., New York 10, Secretary.

Minnesota State Medical Association, Duluth, June 12-14. Dr. B. B. Souster, 496 Lowry Medical Arts Bldg., St. Paul 2, Secretary.

Montana State Medical Association, Bozeman, Gallatin County High School, July 9-12. Dr. Herbert T. Caraway, 115 N. 28th St., Billings, Secretary.

North Dakota State Medical Association, Grand Forks, May 27-30. Dr. O. A. Sedlak, 702 First Ave. S., Fargo, Secretary.

Oklahoma State Medical Association, Oklahoma City, June 4-7. Dr. Lewis J. Moorman, 210 Plaza Court, Oklahoma City, Secretary.

Western Association of Industrial Physicians and Surgeons, San Francisco, June 25. Dr. Christopher Leggo, C. & H. Sugar Refining Corp., Crockett, Calif., Secretary.

Western Branch, American Public Health Association, Portland, Ore., May 30-June 1. Mr. Walter S. Mangold, University of California, Berkeley, Calif., Secretary.

International Meetings

International Anatomical Congress, Oxford, England, July 25-28. Secretary, Miss A. M. Maynall, Department of Human Anatomy, University Museum, Oxford, England.

International Association for the Prevention of Blindness, London, England, July 17-21. Prof. P. Bailliart, 47 rue de Bellechasse, Paris, France, Chairman.

International Cancer Research Congress, Paris, France, July 17-22. Secretariat, 6 Ave. Marceau, Paris 8, France.

International Congress of Ophthalmology, London, England, July 17-21. Mr. Keith Lyle, 45 Lincoln's Inn Fields, London W.C.2, England, Secretary.

International Congress on Asthma, Mont Dore, France, June 3-4. Secretariat, 59 rue Bonaparte, Paris, France.

International Pediatric Congress, Zurich, Switzerland, July 24-28. Dr. L. Emmet Holt Jr., 477 First Ave., New York City 16, Secretary-General.

International Union Against Venereal Diseases, Zurich, Switzerland, July 29-Aug. 2. Dr. A. Cavaillon, Institut A. Fournier, 25 Blvd. St. Jacques, Paris 14em., France, Secretary.

State Legislation

Rhode Island

Bills Introduced.—H. 790 proposes regulations requiring corporations to engage **registered or practical nurses** or first aid workers, depending on the number of employees in the corporation. S. 301 proposes to amend the law relating to **the admissibility of evidence** by providing that a statement of fact or opinion on a subject of science or art contained in a published treatise, periodical, book or pamphlet shall, in the discretion of the court, and if the court finds that it is relevant and that the writer of such statement is recognized in his profession or calling as an expert on the subject, be admissible in actions of contract or tort for malpractice, error or mistake against physicians, surgeons, dentists, optometrists, hospitals and sanatoriums as evidence tending to prove said fact or as opinion evidence. The party intending to offer such evidence, however, would have to give the adverse party notice at least three days before the trial of the action of his intention by stating the name of the writer of the statement and the title of the treatise, periodical, book or pamphlet in which it is contained.

Bills Enacted.—H. 823 was approved April 26, 1950. It amends the **workmen's compensation act** by providing, among other things, that, if any employee refuses to submit to any examination provided for in the act or in any way obstructs such examination, his rights to compensation shall be suspended and his compensation during such period of suspension may be forfeited. S. 265 was approved April 14, 1950. It amends the law relating to medical examiners by, among other things, **increasing the salary of the medical examiner and county medical examiners**, providing for compensation for travel expense of such officials and making the appointment of county medical examiners mandatory rather than permissive.

South Carolina

Bill Enacted.—H. 2579 proposes that **employers in textile mills** shall not require employees who have been absent from their jobs because of sickness to submit to a physical examination before resuming their work, regardless of the number of days which are lost because of sickness, unless the employer shall produce a verified statement of at least two reputable physicians that the sickness of the employee may have impaired his ability to continue to perform his work.

GOVERNMENT SERVICES

PUBLIC HEALTH SERVICE

NEW HILL-BURTON ACT HOSPITALS

The Public Health Service by March 31, 1950 approved a total of 1,224 construction projects for hospitals and health centers under the Hospital Survey and Construction Act. Hospital additions and new hospitals accounted for 1,010 projects, and the remaining 214 were for health centers. The estimated cost of the projects is over $822 million, of which over $282 million will come from federal funds.

The 1,010 hospital construction projects that have received approval thus far would provide 57,852 additional hospital beds. The accompanying tables show the states and territories with the largest number of beds and those with the largest number of health centers.

TABLE 1.—*Number of Approved Hospital Projects*

Texas	70
Mississippi	57
North Carolina	50
New York	49
South Carolina	47
Georgia	41

TABLE 2.—*Number of Additional Hospitals Beds to Be Provided*

Texas	4,005
New York	3,140
Pennsylvania	2,922
Ohio	2,820
North Carolina	2,761
Mississippi	2,674
Puerto Rico	2,224

TABLE 3.—*Number of Approved Health Centers*

South Carolina	45
Mississippi	42
Georgia	29
Louisiana	14
Ohio	10
Virginia	9

There are 163 projects that have been completed, making 3,758 additional beds available, and 45 health centers. As of March 31, projects under construction, 598 in all, included 518 hospital additions or new hospitals and 80 health centers. A total of 31,618 hospital beds will be added by these projects. A total of 463 projects have received initial approval but are still in the blueprint stage.

TUBERCULOSIS SURVEYS

The Tuberculosis Division has reviewed information obtained in the course of taking about 3,500,000 small roentgenograms of the chest during 11 surveys from 1947 through 1949 in which the Public Health Service participated with state and local health departments and community health organizations. The goal in each survey was to reach at least 80 per cent of the population 15 years of age and over. The surveys indicated that 2 to 5 per cent of the small roentgenograms of the chest showed pathologic changes suspected of being tuberculous; 1.3 to 2.8 per cent were suspect for tuberculosis. The comparative incidence of suspected disease was more or less constant for all surveys. Differences in local criteria for interpretation resulted in classification of 20 to 45 per cent of the 14 by 17 inch confirmatory roentgenograms as normal. Of those recalled for 14 by 17 inch roentgenograms, 80 to 92 per cent responded. Tuberculosis suspects found by confirmatory 14 by 17 inch roentgenograms in the surveys comprised consistently close to 1 per cent of the total number of persons screened. Complete diagnoses have not been reported for all suspects found, but available records indicate that about 1 out of every 10 tuberculosis suspects referred for diagnosis have been found to have active disease. Another 2 or 3 out of the 10 have been considered to have lesions requiring further observation and supervision. A greater number of active cases of the disease were found among men than among women, and among older age groups than among the younger ones.

CERTIFIED BY SPECIALTY BOARDS

In addition to those listed in THE JOURNAL May 6, 1950, page 122, the following commissioned medical officers of the Public Health Service have been certified by American specialty boards. This completes the list of commissioned corps personnel certified by specialty boards in 1949.

PREVENTIVE MEDICINE AND PUBLIC HEALTH

Paul W. Kabler, senior surgeon
Max R. Kiesselbach, senior surgeon
Leslie W. Knott, senior surgeon
Frederick W. Kratz, senior surgeon
Vernon B. Link, senior surgeon
John H. Linson, medical director
Jack Masur, medical director
John R. McGibony, medical director
Myron D. Miller, medical director
Benno K. Milmore, surgeon
Paul D. Mossman, medical director
Joseph W. Mountin, assistant surgeon general
Byron J. Olson, medical director
Carroll E. Palmer, medical director
Emil E. Palmquist, medical director
Hildrus A. Poindexter, medical director
John D. Porterfield, surgeon
Arthur B. Price, medical director
Griffith E. Quinby, surgeon
Maurice A. Roe, medical director
Milton I. Roemer, surgeon
Leonard S. Rosenfeld, senior surgeon
Adolph Rumreich, medical director
Leonard A. Scheele, surgeon general
Henry C. Schumacher, medical director
William H. Sebrell Jr., medical director
James K. Shafer, senior surgeon
Charles E. Smith, surgeon
Robert R. Smith, senior surgeon
Ralph B. Snavely, medical director
Paul H. Stevenson, medical director
Russell E. Teague, senior surgeon
James G. Townsend, medical director
Glen S. Usher, senior surgeon
Raymond A. Vonderlehr, medical director
Mary Walton, surgeon
Francis J. Weber, senior surgeon
Hugh C. Wilkerson, medical director
Charles L. Williams Sr., assistant surgeon general
Louis L. Williams Jr., medical director
William G. Workman, medical director
Mark V. Ziegler, medical director

NEUROLOGY AND PSYCHIATRY

James F. Maddux, senior surgeon

SURGERY

James L. Southworth, senior surgeon

FELLOWS FROM JAPAN

Drs. Hideo Kunabe and Tomio Ogata, of Japan, have arrived in the United States for a 90 day training program conducted under a fellowship plan established by the Military Government of Japan. Dr. Kunabe is general manager of the Antituberculosis Association of Japan. He will make a study of tuberculosis control programs in the United States and will also review clinical and research programs. Dr. Ogata is editor in chief of the *Journal of the Japanese Medical Association* and professor of serology at the University of Tokyo Medical School. His training will be concerned with the production of medical and health journals and other publications and the use of medical exhibits and other visual aids.

PERSONAL

Dr. John H. Linson, a medical officer with the Public Health Service for 36 years, will retire April 1. Dr. Linson, a native of Nebraska, received his degree in medicine at Rush Medical College in 1912 and was commissioned in the Public Health Service in 1914.

Dr. Winfield K. Sharp will retire from the Public Health Service on Aug. 1, 1950, after 37 years of service. Dr. Sharp has been detailed to the Alabama State Health Department since February of this year; he will continue to work there after his retirement.

Dr. Marion F. Haralson, medical officer with the Public Health Service for over 30 years, has retired. Since 1947 he has been assigned to the El Paso office of the Pan American Sanitary Bureau, where he has taken part in promoting the general health along the United States-Mexican border.

Medical News

(Physicians will confer a favor by sending for this department items of news of general interest: such as relate to society activities, new hospitals, education and public health. Programs should be received at least two weeks before the date of meeting.)

ALABAMA

The Noland Hospital.—With the unveiling of a bronze plaque before the Employees' Hospital of the Tennessee Coal, Iron and Railroad Company, Fairfield, the name of the late Dr. Lloyd Noland on April 22 became affixed to the institution he founded 30 years ago and directed until his death last year. The speaker at the dedication was Dr. George V. Brindley of Temple, Texas, president of the Southern Surgical Association. Messages from Benjamin F. Fairless, president of U. S. Steel Corporation, and Dr. Ernest E. Irons, President of the American Medical Association, were read at the ceremony. Dr. Noland came to the Birmingham district in 1913 to assume the task of improving the health situation among TCI employees. Under his direction a health service was set up which reached all company villages and which in a few years greatly reduced the incidence of infectious diseases. Built under Dr. Noland's supervision, the 350 bed hospital which now bears his name was completed in 1919. It has complete medical, surgical and dental facilities for the company's more than 30,000 employees and their families.

CALIFORNIA

Surgeons Establish Research Fund.—A $3,500 research fund has been presented to the department of surgery of the University of California Medical School, Los Angeles, by the Bay District Surgical Society. The society is made up of a group of Santa Monica, Beverly Hills and Los Angeles surgeons. The fund will be used to set up a program for the investigation of diseases of the heart and lungs but primarily directed toward heart diseases resulting from rheumatic fever. Members of the staff of the medical school and the Wadsworth General Hospital, West Los Angeles, will cooperate in the study. The program will be initiated in the temporary buildings of the medical school. It will be transferred to the teaching hospital on completion of the new medical center.

COLORADO

Course in Cytologic Diagnosis of Cancer.—A course in exfoliative cytology for the diagnosis of cancer by the smear technic will be offered at the University of Colorado School of Medicine, Denver, for qualified physicians. The class will meet daily for two weeks, beginning July 24 and ending August 5. Material will be available for study with correlation of clinical, roentgen and pathologic findings. Members of the staff of the medical school and associated hospitals will cooperate in presenting the course. The tuition is $100. Physicians interested should write Walter T. Wikle, M.D., Director, Laboratory of Exfoliative Cytology, University of Colorado School of Medicine, 4200 East Ninth Avenue, Denver 7.

CONNECTICUT

Personal.—The National Society for the Prevention of Blindness has awarded a grant to Dr. Eugene M. Blake of the department of ophthalmology, Yale University School of Medicine, New Haven, for a study of pituitary adrenocorticotropic hormone (ACTH) in the treatment of glaucoma.

Appoint Director of Hospital Administration.—Mr. George S. Buis, assistant executive secretary of the American College of Hospital Administrators in Chicago, has been appointed director of the program in hospital administration at Yale University, New Haven, effective July 1, succeeding Dr. Clement C. Clay, who organized the Yale program in 1947. Mr. Buis is a former superintendent of Brackenridge Hospital in Austin, Texas. Since 1946 he has directed many of the institutes conducted by the American College of Hospital Administrators. A graduate of the University of Iowa, Mr. Buis in 1935-1936 held a Rosenwald Fellowship in Hospital Administration at the University of Chicago, where he received a master's degree in business administration in 1937.

State Medical Election.—Dr. Thomas J. Danaher, Torrington, assumed office as president of the Connecticut State Medical Society during its recent annual meeting in Waterbury. Dr. Danaher succeeds Dr. Charles H. Sprague of Bridgeport. Dr. C. Charles Burlingame, Hartford, was named president-elect, Dr. F. Brae Rafferty, Willimantic, first vice president, and Dr. J. Howard Staub, Stamford, second vice president. Dr. Cole B. Gibson, Meriden, was reelected treasurer; Dr. Creighton Barker, New Haven, executive secretary; Dr. Stanley B. Weld, Hartford, editor of the *Connecticut State Medical Journal*, and Dr. Herbert Thoms, New Haven, literary editor.

ILLINOIS

Society News.—At a meeting of the Illinois Association of Medical Health Officers held recently in Springfield the following officers were elected for 1950-1951: president, Dr. Samuel N. Mallison of District Health Office No. 6, Champaign; vice president, Dr. Leroy L. Fatherree of the Will County Health Department, Joliet, and secretary-treasurer, Dr. Herbert S. Ratner, health commissioner of Oak Park.

Chicago

Personal.—Lieut. Col. James D. Majarakis has been appointed executive officer of the 427th General Hospital, a 1,000 bed U. S. Army reserve unit which is sponsored by the University of Illinois College of Medicine. During World War II he served as chief of a surgical team.

Medical Scholarships.—Two subsidiary scholarships, amounting to $10,000 each, have been given to the Chicago Medical School. One in honor of Mrs. Mary Feinberg of Allentown, Pa., and Miami Beach, Fla., has been given by Mr. Jacob Feinberg and family. The other, given by an anonymous donor of Miami Beach, is in honor of Mrs. Milton S. Saslow, Howard A. Engle and Morris Blau, all of that city.

Appointment to Institution for Tuberculosis Research.—Dr. Stanley W. Olson, dean of the University of Illinois School of Medicine, has been appointed by the University of Illinois Board of Trustees to the Board of Directors of the Institution for Tuberculosis Research, to fill the vacancy on the five man board. The Institution for Tuberculosis Research was established by the Sixty-Sixth General Assembly of Illinois for the production, distribution and application of BCG and other methods and materials for the prevention of tuberculosis and for conducting research in tuberculosis.

New Dermatologic Society.—A group of dermatologists practicing in the Chicago area formed the Metropolitan Dermatological Society of Chicago, incorporated under the laws of Illinois, on March 15. Qualification for fellowship is board certification. Associate membership is limited to those eligible for board examination. Meetings will be held on the second Wednesday of each month from October through May. Place of the meetings will be the dermatologic services of the fellows in alternation. The present officers are: Drs. Theodore K. Lawless, president; Irving M. Cobin, Joliet, vice president, and Tibor Benedek, secretary-treasurer.

New Department of Public Health.—Howard J. Shaughnessy, Ph.D., professor of bacteriology since 1943 and chief of the division of laboratories of the Illinois Department of Public Health, has been appointed professor and head of the newly created department of public health at the University of Illinois College of Medicine, effective June 1. He will continue to serve as director of laboratories of the state department. The university will offer graduate instruction in public health leading to a master of science degree. The university plans eventually to train specialists in public health administration, health education, nursing, nutrition, laboratory practice, statistics, engineering, as well as epidemiology, venereal disease control, tuberculosis control, school health, industrial health and sanitary science. A program of research also will be undertaken by the department.

INDIANA

Course in Microbiology.—The third annual Industrial Microbiology short course will be held on the Purdue University campus in Lafayette June 19 to July 1. An intensive two week program is being planned for research and production directors in microbiology laboratories and for technicians, as well as a refresher course for college teachers and research workers. Additional information may be obtained from Charles L. Porter, Ph.D., School of Science, Purdue University, Lafayette.

IOWA

Public Meeting on British Medical Practice.—The Dubuque County Medical Society on May 10 was host at a dinner to more than 200 persons representing labor unions, civic and church groups, dentistry, nursing, pharmacy and law. After dinner the guests and the general public met at the senior high school auditorium, where, under the sponsorship of the medical society and the Dubuque Adult Educational Forum, an open forum was held on the British system of medical practice. Guest

speakers were Dr. Ralph J. Gampell of San Francisco, formerly from Manchester, England, and Mrs. Molly Moon Samore of Sioux City, formerly from Lancastershire, England. Dr. Gampell spoke on "Medical Practice Under the British System," and Mrs. Samore, "The Patient Under the British Scheme."

MICHIGAN

Course in Industrial Hygiene and Human Relations.—The University of Michigan School of Public Health, Ann Arbor, is offering an inservice training course in Industrial Hygiene and Human Relations for Safety Personnel on June 19-21. The subjects covered will include sanitation, plant layout, plant skin hazards and industrial health hazards, such as toxic metals, dusts and gases. This course is designed for all those responsible for safety. However, all interested persons are invited to attend. Application for enrolment should be addressed to H. E. Miller, School of Public Health, 109 South Observatory Street, Ann Arbor, Mich. The fee is $5.

Cancer Clinic Opens.—A cancer control clinic under the joint auspices of the American Cancer Society, the Detroit Institute of Cancer Research and Wayne University and staffed by Wayne University College of Medicine was opened May 1 in the American Cancer Society Building, John R and East Hancock streets. The service will extend to all persons free of charge. The clinic will not accept for examination any patient in whom the diagnosis of cancer has been made, nor will any treatment be given. Information will be forwarded to the patient's own physician. Appointments may be made on Monday, Wednesday and Thursday from 3 to 5 p. m. and on Tuesday from 7 to 9 p. m. The clinic is to serve also as a training facility for members of the medical profession. Beginning July 1, a limited number of qualified doctors of medicine may enroll for the summer quarter in a special class of cancer diagnosis. Regular enrolment for the fall quarter will be accepted at this time by the dean of the college of medicine. The tuition is $50 per quarter.

NEW YORK

Personals.—Dr. Gerald B. Manley of Geneseo has been appointed a member of the Public Health Council, succeeding Dr. Walter A. Leonard, Cambridge, who has been a member since 1932. Dr. Manley is health officer of the Consolidated District, Town of Leicester, and chairman of the Livingston County Public Health Committee.——Dr. F. Robert Freckleton, deputy commissioner, Rensselaer County Health Department since 1947, has been appointed commissioner of the Columbia County Health Department. He is a graduate of Tulane University of Louisiana School of Medicine, New Orleans.——Dr. Frederick S. Wetherell, editor and founder of the *Bulletin of the Onondaga County Medical Society and the Syracuse Academy of Medicine*, has resigned after 14 years' service.

Augustus B. Wadsworth Lecture.—Dr. Warfield T. Longcope, emeritus professor of medicine, Johns Hopkins University School of Medicine, Baltimore, presented the first Augustus B. Wadsworth Lecture, on "Clinical Implications of Recent Advances in the Medical Sciences," in Albany May 24. The lectureship has been established by the staff of the Division of Laboratories and Research of the New York State Department of Health and the Council of the New York State Association of Public Health Laboratories. Dr. Wadsworth retired as director of the Division of Laboratories and Research in 1945 after 31 years' continuous service. He is a graduate of the Massachusetts Institute of Technology, Cambridge, and of the Columbia University College of Physicians and Surgeons, New York.

New York City

Lay Cornerstone for Institute.—Cornerstone-laying ceremonies were held May 24 for the Institute of Physical Medicine and Rehabilitation, the first unit in the new university section of the New York University-Bellevue Medical Center. The building will be ready for occupancy late this year.

Course in Occupational Skin Diseases.—Representatives of labor, industry and the New York State Workmen's Compensation Board will cooperate with the faculty of New York University Post-Graduate Medical School to give a two week intensive course in "Occupational Dermatoses" June 5-16. The course, to be presented jointly by the medical school's departments of dermatology and syphilology, and industrial medicine, under the auspices of the Institute of Industrial Medicine of the New York University-Bellevue Medical Center, will consist of lectures and demonstrations designed to provide basic instruction in major problems relating to industrial skin diseases. Sessions will be held in Erdmann Auditorium, University Hospital, 303 East 20th Street, and the Pathology Lecture Room of the Skin and Cancer Unit of the Medical Center, 330 Second Avenue. Applications should be directed to the Office of the Dean, New York University Post-Graduate Medical School, 477 First Avenue, New York 16.

Mental Hygiene Services Report.—Dr. John F. Mahoney, health commissioner, released a report April 22 embodying recommendations resulting from a study of mental hygiene in relation to the work of the department made by Dr. Jules V. Coleman, former associate professor of psychiatry, University of Colorado Medical School. The study was financed by a grant from the New York Foundation, Inc. The recommendations center about the concept that the department should concern itself with the emotional problems of persons served by the department rather than with establishing specialized clinics for the care and treatment of the occasional patient with neurotic or psychotic disorders. In the operation of a mental hygiene program, the report said, special attention should be given to work in the department's 74 child health stations, which serve 100,000 infants and preschool children. It was recommended that at least half of the effort put into any mental hygiene work be devoted to child health services. The report emphasized that the greatest help can be given patients by present members of the health department staff in their regular contacts with patients. Therefore Dr. Coleman recommended training present professional staff members, particularly doctors and nurses, in the fundamentals of mental hygiene and the handling of emotional and personality difficulties.

OHIO

Professor Crafts to Head Anatomy Department.—Now a faculty member of the department of anatomy of the Boston University School of Medicine, Roger C. Crafts, Ph.D., has been appointed head of the same department in the University of Cincinnati College of Medicine, effective June 1. Dr. Crafts will fill the Francis Brunning chair of anatomy, succeeding Joseph L. Schwind, Ph.D., who died in 1948. Born in 1911 in Maine, Dr. Crafts received the bachelor of science degree in 1933 from Bates College there. He taught at the College of Physicians and Surgeons, Columbia University, New York, from 1939 to 1940, when he received the doctor of philosophy degree. Going to Boston University in 1941, he held the rank of assistant professor of anatomy for two years, then was promoted to the rank of associate professor. During the war he was with the Office of Naval Research.

PENNSYLVANIA

Air Pollution Mobile Unit.—The Pennsylvania Department of Health has secured an air pollution and industrial hygiene laboratory, which will be placed in service by the Bureau of Industrial Hygiene. The mobile unit is equipped with more than 25 scientific devices for field sampling and quantitative and qualitative analyses of atmosphere in industrial communities and factories. The mobile laboratory will be under the supervision of the state's new Air Pollution Division, Pittsburgh Laboratory.

Philadelphia

Society News.—At the annual business meeting of the Philadelphia Laryngological Society on May 2, the following officers were elected for the coming year: Drs. Thomas F. Furlong Jr., Ardmore, Pa., president; Harry P. Schenck, vice president; William J. Hitschler, treasurer, and John J. O'Keefe, secretary.

Alumni Clinics.—The Medical Alumni Society of the University of Pennsylvania will hold medical and surgical clinics at the University Hospital from 9:30 a. m. to 11:30 a. m. on Alumni Day, June 17. After the clinics the society will have luncheon at the Penn-Sheraton Hotel. Information may be obtained from Miss Frances R. Houston, executive secretary, Medical Alumni Society, University of Pennsylvania School of Medicine.

Personals.—At a recent meeting of the Board of Trustees of the Philadelphia College of Pharmacy and Science Dr. Leonard D. Frescoln was elected a trustee of the college.——Dr. S. Clyde Strickland has been appointed a staff physician in the Sharp and Dohme Medical Division in Philadelphia. A native of New Glasgow, Nova Scotia, Canada, his duties with the Medical Division will be to conduct clinical investigations on new products developed by the Medical Research Division.

Pittsburgh

Postgraduate Symposium.—The University of Pittsburgh School of Medicine will present a postgraduate symposium on Basic Sciences Related to Anesthesiology June 19-23 in cooperation with the departments of anesthesiology of St. Francis, Allegheny General and Mercy hospitals. The course will be limited to 30 participants, and the fee is $25. Information may be obtained from the Chairman, Committee on Graduate Medical Education, University of Pittsburgh School of Medicine.

UTAH

Mental Health Institute.—A Mental Health Institute for Public Health Physicians of the ten state Intermountain area will be held in Salt Lake City under the auspices of the Department of Psychiatry of the University of Utah School of Medicine, Salt Lake City, June 12-22. This institute has been made possible by a grant from the U. S. Public Health Service. The dean of the faculty will be Dr. Jules V. Coleman, associate professor of psychiatry at the University of Colorado School of Medicine, Denver. Other faculty members will be Dr. Earl D. Bond, professor emeritus of psychiatry, University of Pennsylvania School of Medicine, Philadelphia, Dr. Edward D. Greenwood, director of Children's Division, Menninger Foundation, Topeka, Kan., Dr. Frederick C. Redlich, professor of psychiatry, Yale University School of Medicine, New Haven, Conn.; Dr. Winfield S. Wilder, of Great Falls (Mont.) Mental Hygiene Clinic; Dr. James A. Crabtree, professor of public health practice, University of Pittsburgh, Graduate School of Public Health; Dr. Hyrum L. Marshall, professor of public health and preventive medicine and acting dean of the University of Utah College of Medicine, and Dr. Estella Ford Warner, U. S. Public Health Service, Washington, D. C. Members of the University of Utah department of psychiatry who will be faculty members include Drs. Charles H. Branch and Dr. Leonard H. Taboroff, Topeka, Kan.

VIRGINIA

Dr. Hagood to Receive Honorary Degree.—Dr. James D. Hagood will be awarded an honorary master of science degree in general medicine at the Commencement program of the Medical College of Virginia on June 6. This is a new degree established by the college to give recognition to the importance of the general practice phase of medicine. Dr. Hagood was chosen by the college as the first recipient of the degree. He was selected Virginia practitioner of the year 1948 and is now president of the Virginia Academy of General Practice.

WASHINGTON

Internists Meet in Spokane.—The first annual meeting of the newly organized Spokane Society of Internal Medicine was held at the Spokane City Club May 13. Dr. Robert H. Williams, professor and executive officer of the department of medicine, University of Washington, Seattle, was the guest speaker. His subjects were "Therapy of Pyelonephritis with Special Consideration of Its Pathologic Physiology" and "Recent Advances in Physiology of the Thyroid and in Treatment of Its Disorders." Additional papers and panel discussions were presented by members of the society. At the evening banquet Dr. Williams discussed "Recent Developments and Future Plans of the Department of Medicine of the University of Washington."

WISCONSIN

Dr. Eberbach to Direct Department of Surgery.—Dr. Carl W. Eberbach has been made director of the department of general surgery at Marquette University School of Medicine, Milwaukee, succeeding Dr. Frederick A. Stratton, who retired (THE JOURNAL, January 28, page 268) after 43 years at the university. Dr. Eberbach was chief of staff at Milwaukee Passavant Hospital and president of the Wisconsin Surgical Society. He graduated from the University of Michigan Medical School, Ann Arbor, in 1916. He was a resident instructor and assistant professor of surgery at Michigan from 1920 to 1927, when he joined the faculty of Marquette.

Symposium on Malignant Diseases.—The University of Wisconsin Medical School, Madison, will present a postgraduate symposium on malignant diseases in the auditorium of the Service Memorial Institutes Building June 20-22. The subject will be covered from the standpoint of the various diagnostic technics. Included also will be discussion of the technic and limitations of the Papanicolaou Cytologic Diagnostic Method. The faculty will include distinguished speakers from outside the state as well as members of the medical school. Registration may be made in advance by mail. Tuition fees for the course, $25, should be made payable to the University of Wisconsin. All inquiries should be addressed to the University of Wisconsin Medical School, 418 North Randall Avenue, Madison 6.

GENERAL

International Congress on Microbiology.—The fifth International Congress on Microbiology will be held at Rio de Janeiro, August 17-24. The fiftieth anniversary of the Oswaldo Cruz Institute will be celebrated at the same time. The secretary general is Dr. Joaquim Travassos, Instituto Oswaldo Cruz, Caixa Postal 926, Rio de Janeiro, Brazil.

Editor Retires.—With the February issue of the *Journal of Comparative Neurology* Dr. Gerhardt von Bonin, Chicago, took over as managing editor, replacing Davenport Hooker, D.Sc., Pittsburgh, editor since 1933, who retired. Manuscripts originating in the Western Hemisphere should be sent to Dr. von Bonin at the University of Illinois College of Medicine, 1853 West Polk Street, Chicago 12.

Distribution of Medical Journals for Foreign Relief.—The Educational Reconstruction Committee of the American Council of Voluntary Agencies for Foreign Service, Inc., as a part of their work as a clearing house agency, will accept for placement files of medical magazines which physicians may wish to donate for foreign relief. Through its service the Unitarian Service Committee and the Greek War Relief Association have accepted such files for their voluntary agencies.

Directory of Medical Illustrators.—The directory issue of *Graphics*, the official publication of the Association of Medical Illustrators, contains the name, address, training, professional experience and reference to major published work of each member. Other information pertaining to the profession is included. The journal, to be issued on June 1, will be available to those requiring medical illustration service and will be sent free of charge on request to the editor, Miss Helen Lorraine, 5212 Sylvan Road, Richmond 25, Va.

First Medical Regiment Reunion.—Former members of the regiment are urged to join in the first big reunion to be held during the American Medical Association meeting in San Francisco, June 26-30. Make plans now to attend the convention and this reunion at the Claremont Hotel, Berkeley, Wednesday, June 28, 1950. Cocktails—6:30; Dinner—8:00, $3.50 per plate. Send reservation and check to: Charles B. Hudson, M.D., 400 29th Street, Oakland 9, Calif.

Imposter.—A "Dr. Benton of Baltimore," reportedly posing as president of the Maryland Society for the Prevention of Blindness, recently called at the office of the Minnesota Society for the Prevention of Blindness. After gaining confidence through a comparison of the state program with that of Maryland, he cashed a $40 check, drawn on the Equitable Trust of Baltimore, in the office of one of the physicians in the building. The check was returned marked "signature illegible." Investigation by the Minnesota society proved that "Dr. Benton's" story was not true.

Medical Historians Meeting.—The American Association of the History of Medicine held its annual meeting at the Somerset Hotel, Boston, May 21-23. The one-hundredth anniversary of the birth of Dr. William Henry Welch, founder of the Johns Hopkins University School of Medicine and the School of Hygiene and Public Health, Baltimore, was observed Sunday with appropriate papers. The Fielding H. Garrison Lecture was presented by Roland H. Bainton, Ph.D., New Haven, Conn., on "Michael Servetus, Physician." At the dinner Monday evening George Sarton, LL.D., Harvard University, spoke on "Robert Boyle—the Sceptical Chymist."

Western Industrial Physicians Meeting.—The Western Association of Industrial Physicians and Surgeons invites all American Medical Association members to attend its meeting on June 25 from 9 a. m. to 5 p. m. in the Curran Theater, 455 Geary Street, San Francisco. The program includes: Tetanus Prophylaxis in Previously Immunized Persons, Dr. Rodney R. Beard, San Francisco; Medical Administrative Problems in Workmens Compensation Cases, a panel; A Rest Regimen for Acute Back Sprain, Drs. R. Christopher Leggo, Crockett, Calif., and Harry R. Walker, Oakland, Calif.; Psychosis, a Side Door out of Industry, Dr. Frank F. Tallman, Sacramento, Calif., and Job Placement in the Rehabilitation of Alcoholics, a panel.

International Congress of Surgery.—The Seventh International Congress of Surgery will be held at Buenos Aires on August 1-5 at the headquarters of the Faculty of Medical Sciences and Dentistry under the auspices of the Argentine government. It is organized by the Argentine Chapter of the International College of Surgeons of Geneva, Switzerland, under the chairmanship of Dr. Carlos I. Rivas, who presides also as chairman of the Executive Committee of the Congress. An invitation is extended to contribute to the congress with

scientific work and to send an American delegation. Information can be obtained from Exprinter S. A., San Martin 176, Buenos Aires, and All Nations Travel Bureau, 38 South Dearborn Street, Chicago.

Course for Orthoptic Technicians.—The American Orthoptic Council will present its third annual training course for orthoptic technicians beginning July 5 in Boston. This course was given in Maine in 1948 and in Boston in 1949. The didactic portion will last through August 30, the tuition fee being $150 and room and board $100, and the practical portion will be given in various teaching clinics and offices throughout the country during the succeeding year. Ophthalmologists and certified orthoptic technicians will aid Dr. Walter B. Lancaster, Boston, with the didactic instruction. Scholarships for worthy students may be available. Information may be obtained from the office of the American Orthoptic Council, 1605 22nd Street, N. W., Washington 8, D. C. The deadline for receipt of applications is July 1.

WHO Committee on Hospital Statistics.—Dr. Edwin L. Crosby, director of the Johns Hopkins Hospital, has been appointed United States representative to a World Health Organization committee on hospital statistics. The new committee was established in accordance with instructions received from the Second World Health Assembly. As a subcommittee to the Expert Committee on Health Statistics it will initiate proper action in the field of hospital statistics, with primary attention given to the new international statistical classification of diseases, injuries and causes of death. Appropriate questions will be prepared for submission to national committees on health statistics. Dr. Crosby is with the U. S. Veterans Administration and the U. S. Public Health Service. In addition to his hospital appointment, he is chairman of the Council on Professional Practice of the American Hospital Association.

American Academy of Tuberculosis Physicians Meeting.—The annual meeting of this academy will be held at the Palace Hotel, San Francisco, June 24. The program is as follows:

Jacob W. Cutler, Philadelphia, Importance of Extrapleural Pneumothorax in the Collapse Therapy of Pulmonary Tuberculosis.
Paul C. Samson, Oakland, Calif., Decortication in Pulmonary Tuberculosis.
Ralph Adams, Woodbury, Tenn., Resection in Pulmonary Tuberculosis.
Joseph M. Goorwitch, Los Angeles, Extrapleural Plombage.
C. Richard Smith, Los Angeles, Bacteriology Versus Roentgenology in the Diagnosis and Treatment of Pulmonary Tuberculosis.
Samuel E. Hughes Jr., Downey, Ill., Pneumoperitoneum in the Treatment of Pulmonary Tuberculosis.
Hamilton H. Anderson, San Francisco, Influence of Antituberculous Agents on Oxygen Consumption of Mycobacteria.
Emil Bogen, Olive View, Calif., Effect of Neomycin in Tuberculosis, in Culture Mediums, in Guinea Pigs and in Patients.
David Salkin, San Fernando, Calif., Empyema Following Closed Intrapleural Pneumonolysis.
Raymond H. Rigdon, Galveston, Texas, Necrosis of the Basal Nuclei in Cases of Tuberculous Meningitis Treated with Streptomycin.
J. P. Myles Black, Olive View, Calif., Clinical Evaluation of the Use of Paraaminosalicylic Acid (PAS) with Streptomycin.
Elliott P. Smart, Murphys, Calif., Present Status of over 10 Years' Experience with Extrapleural Pneumothorax.
Maurice G. Buckles, Columbus, Ohio, Bronchiectasis and Tuberculous Bronchitis.
Harry J. Corper, Denver, Growth of Tubercle Bacilli at Suboptimum Temperatures.

Science Writers Awards.—For the best writing on medical science and public health, awards of $500 and statuettes of the Winged Victory of Samothrace were presented at the dinner of the National Association of Science Writers in April. The winners were Herbert and Dixie Leppert Yahraes in the magazine field for their article in *Collier's*, "Our Daughter is an Epileptic," and William L. Laurence of the *New York Times* in the newspaper field for his work on the development of cortisone and pituitary adrenocorticotropic hormone (ACTH). These were the first Albert and Mary Lasker Awards made in the field of journalism. Previous winners had been medical researchers and public health proponents. The Nieman Foundation for Journalism administered the awards. Mr. and Mrs. Yahraes are veteran newspaper and free lance writers. They are cited "for their achievement in most usefully disseminating the fruits of medical research; for appealing powerfully to the public conscience by stressing the opportunity and responsibility of the community toward the health of individual sufferers, for skilful and poignant narrative and for their courage in setting aside personal reticence to make their experience a challenge and a light to their fellow-men." Mr. Laurence was cited "for his alertness and instant grasp in presenting to the public these discoveries which rank among the most significant of the year; for his initiative in using his own research as a reporter to furnish a valuable lead in the further development of cortisone; for his clarity of perception and of style, and for his disciplined judgment which insisted upon accuracy and restraint in dealing with the most urgent of subjects."

FOREIGN

British Radiographers Conference.—The Society of Radiographers, which is affiliated with the British Institute of Radiology in London, will hold its fourth annual conference in Edinburgh June 22-24 at the North British Station Hotel. The following lectures will be given: Some Aspects of Radiography and Rheumatism, Recent Advances in Apparatus, Value of Supplementary Views in Radiography, Aids to Radiographic Definition and Radiological Recognition of the Spread of Cancer.

Courses in Occupational Health and Rehabilitation.—Roffey Park Rehabilitation Centre, Horsham, Sussex, England, is offering two international courses on Occupational Health and Rehabilitation July 17-24 and August 14-21. Industrial physicians, personnel managers, welfare workers and senior nursing administrators are welcome. The course is arranged to provide an understanding of individual and group health based on current psychologic principles. Adequate time is available for informal discussions. Visitors are housed in an attractive licensed residential club in the grounds. Applications for vacancies should be made to the Secretary, Roffey Park, Horsham, Sussex, England, stating the preferred week. The fee, which includes tuition and full residence, is $30.

Outbreak of Cholera in India.—Information has reached the World Health Organization's Headquarters in Geneva, Switzerland, that cholera cases and deaths have been steadily rising in Calcutta, India, since the early part of March. In that city 3,311 cholera cases with 1,233 deaths were reported from January 1 to April 13. This appears to be the most serious outbreak of cholera in India since 1943, when 7,007 cases occurred in Calcutta. Normally, the World Health Organization explained, the curve of incidence falls off sharply during July and August with the coming of heavy rains. During the past thirty years the annual number of cholera cases in Calcutta has never fallen below 1,800. Apart from the seasonal rise in incidence, the influx of refugees appears to be a factor in the present outbreak.

International Training Center for Anesthetists.—The first international center for study of modern technics of anesthesiology opened May 3 at the Rigshospital in Copenhagen as a cooperative enterprise of the Faculty of Medicine in Copenhagen University and the World Health Organization. The center will provide a one year postgraduate course for physicians and surgeons of Scandinavian and other European countries in modern developments in anesthesiology. The course will open with two American specialists acting as senior instructors and advisers. They are Dr. Stuart C. Cullen, State University of Iowa College of Medicine, Iowa City, and Dr. Ralph M. Waters, retired professor of anesthesia, University of Wisconsin, Madison. A British specialist, Dr. Phyllis Edwards, and several Danish doctors will be junior instructors. WHO will provide supplies and fellowships for 21 medical graduates from Sweden, Norway, Finland, Iceland, Austria, Yugoslavia and Denmark.

Tuberculosis Centers in Southeast Asia.—Plans have been made for establishment by WHO and the United Nations International Children's Emergency Fund of three tuberculosis centers in India to be followed by other centers in Burma, Ceylon and Thailand. WHO has appointed Dr. Edmond McWeeney of Dublin as tuberculosis adviser for the region. The Indian Health Ministry grants to the Tuberculosis Association are for the construction of centers. Meanwhile, plans are proceeding for development of existing antituberculosis centers at Colombo and Rangoon. Primary functions of the WHO-UNICEF tuberculosis center will be training of medical and technical personnel in modern methods of prevention, diagnosis and treatment. Each center will have as its nucleus a clinic with a small number of beds and a laboratory and a mobile dispensary, designed to serve rural areas and equipped to give accurate diagnosis. Supplies and part of the international staff will be furnished by UNICEF, and technical guidance will be provided by WHO.

Marriages

LUTHER RANDOLPH STINSON, Scottsville, Va., to Miss Arleen Foushee Boyce of Howardsville, March 24.

JAMES GORDON HALFORD JR., Johnston, S. C., to Miss Marjorie Ruth Gault in Greenwood, April 14.

EDGAR COLEY GARRARD, Catawba Sanatorium, Va., to Miss Mary Elizabeth Slater in Salem, April 14.

JOHN MARION BABICH to DR. MARIE ELIZABETH DUGAS, both of Sacramento, Calif., April 15.

Deaths

James Millington Brown ✦ Medical Director, Captain, U. S. Navy, retired, Long Beach, Calif.; born in 1894; St. Louis University School of Medicine, 1916; entered the U. S. Navy on Oct. 19, 1917; after serving in World War I began practice in St. Louis, where he was assistant professor of clinical pediatrics at his alma mater, visiting physician at the Missouri Pacific Hospital from 1920 to 1924, assistant pediatrician to St. Mary's Group of Hospitals from 1925 to 1927 and from 1933 to 1942, when he became associate pediatrician and assistant pediatrician to St. John's Hospital; member of the American Medical Association and Missouri State Medical Association; began active duty in 1940; served aboard the U.S.S. *Chandeleur*, during World War II in the Pacific; in 1945 became senior medical officer at the Naval Air Station at Lambert-St. Louis Municipal Airport, where he remained until 1947, when he was assigned to the U. S. Naval Hospital in San Diego; retired Oct. 1, 1949; died March 22, aged 56, of heart disease.

John Francis Kenney, Pawtucket, R. I.; born in New Bedford, Mass., Jan. 5, 1890; Tufts College Medical School, Boston, 1913; specialist certified by the American Board of Internal Medicine; fellow of the American College of Physicians; member of the American Association of Industrial Physicians and Surgeons and the American Medical Association; past president of the Rhode Island Medical Society and the New England Conference of Industrial Physicians; member of the Board of Medical Examiners in the Basic Sciences; affiliated with Memorial Hospital; on the staff of the St. Joseph's Hospital; consulting physician, Lying-In Hospital, Jane Brown Memorial Hospital and the Rhode Island Hospital, all in Providence; consulting physician at the Sturdy Memorial Hospital in Attleboro, Mass., State Sanatorium, Wallum Lake and State Hospital, Howard; died March 20, aged 60, of coronary thrombosis.

Ray Bardwell McCarty ✦ Riverside, Calif.; born in Corona, Calif., Sept. 1, 1899; University of Pennsylvania School of Medicine, Philadelphia, 1925; received the degree of M.S. in surgery from the University of Minnesota Graduate School, Minneapolis-Rochester, 1930; specialist certified by the American Board of Surgery; member of the Pacific Coast Surgical Association; fellow of the American College of Surgeons; on Oct. 1, 1927 became a fellow in surgery at the Mayo Foundation in Rochester, Minn., where he was resident surgeon at the Colonial Hospital from October 1930 to October 1931; served during World War II; affiliated with Riverside Community and Riverside County hospitals; died April 15, aged 50, of cardiac insufficiency.

David Washburn Wells, Newton, Mass.; born in West Newton, Mass., in 1862; Boston University School of Medicine, 1897; professor emeritus of ophthalmology at his alma mater; specialist certified by the American Board of Ophthalmology; member of the American Academy of Ophthalmology and Otolaryngology, American Medical Association and the New England Ophthalmological Society; fellow of the American College of Surgeons; past president of the New England Ophthalmological Society; for many years affiliated with Massachusetts Memorial Hospitals in Boston and Newton Hospital; author of "Psychology Applied to Medicine," 1907, and "Stereoscopic Ophthalmology"; died March 4, aged 87, of coronary thrombosis.

Herbert Noble Vermilye ✦ Forest Hills, N. Y.; born in Anniston, Ala., Nov. 16, 1887; Columbia University College of Physicians and Surgeons, New York, 1914; specialist certified by the American Board of Internal Medicine; fellow of the American College of Physicians and the American College of Allergists; member of the Harvey Society, Omega Society, New York Rheumatism Association and New York Psychiatric Association; served during World War I with the Presbyterian Hospital Medical Unit in France, attaining the rank of major; formerly affiliated with Presbyterian Hospital and Fifth Avenue Hospital; died April 12, aged 62, of heart disease.

William Anderson, Price, Utah; College of Physicians and Surgeons, Baltimore, 1910; died March 29, aged 75, of carcinoma.

William Sidney Austin ✦ Knoxville, Tenn.; University of Pennsylvania Department of Medicine, Philadelphia, 1899; past president of the Knox County Medical Society; at one time a member of the city board of education; affiliated with St. Mary's, Knoxville General and Fort Sanders hospitals; associate surgeon for the Southern Railway and the Louisville and Nashville Railroad; died April 10, aged 74, of leukemia.

Walter Thomas Bailey, Indianapolis; Meharry Medical College, Nashville, Tenn., 1910; died in Marion, Ind., February 10, aged 64, of cerebral hemorrhage and hypertension.

Edward L. Beal, Republic, Mo.; Jefferson Medical College of Philadelphia, 1888; died in the Springfield Baptist Hospital, Springfield, March 25, aged 86, of bronchopneumonia and carcinoma of the prostate.

Joseph Howard Beard ✦ Champaign, Ill.; Johns Hopkins University School of Medicine, Baltimore, 1912; specialist certified by the American Board of Preventive Medicine and Public Health; member of the American Public Health Association; professor of hygiene, organized and became director of the university health service, university health officer and medical director of the university retirement system at the University of Illinois; died in McKinley Hospital, Urbana, April 5, aged 67, of coronary occlusion.

John A. Bentley, Allen, Okla. (licensed in Oklahoma under the Act of 1908); died February 27, aged 77, of cerebral hemorrhage.

David Franklin Berry, Indianapolis; Central College of Physicians and Surgeons, Indianapolis, 1900; member of the American Medical Association and the American Academy of Ophthalmology and Otolaryngology; specialist certified by the American Board of Otolaryngology; affiliated with City and Methodist hospitals; died March 16, aged 75, of coronary occlusion.

Irvin Edwin Booher ✦ Connersville, Ind.; University of Louisville (Ky.) Medical Department, 1913; past president of Fayette-Franklin Counties Medical Society; served during World War I; secretary of the board of health of Connersville; first president of the Fayette Memorial Hospital medical staff; died March 15, aged 67, of coronary occlusion.

William Roscoe Boone, Berkeley, Calif.; Oakland College of Medicine and Surgery, 1912; member of the American Medical Association; affiliated with Alta Bates and Herrick Memorial hospitals; died March 21, aged 65, of coronary occlusion.

Frank Joseph Briglia ✦ Philadelphia; Jefferson Medical College of Philadelphia, 1928; member of the American Academy of Ophthalmology and Otolaryngology; specialist certified by the American Board of Otolaryngology; served during World War II; instructor in laryngology at the University of Pennsylvania Graduate School of Medicine; affiliated with the Graduate Hospital of the University of Pennsylvania; died April 5, aged 46, of heart disease.

Andrew Morton Carr Jr., Minot, N. D.; Rush Medical College, Chicago, 1915; member of the American Medical Association; served overseas during World War I; formerly on the staff of Trinity Hospital; died March 15, aged 59, of heart disease.

Clarence Thomas Carr, La Grange, Ill.; Hering Medical College, Chicago, 1902; member of the American Medical Association; for many years mayor of Somonauk; affiliated with the Hinsdale (Ill.) Sanitarium and Hospital; died March 28, aged 72, of acute coronary disease.

John Godfry Chaloupka, Omaha; Creighton University School of Medicine, Omaha, 1922; served on the staffs of St. Joseph's and St. Catherine's hospitals; died April 4, aged 53, of heart disease.

James Ryle Coffey, New Haven, Conn.; Yale University School of Medicine, New Haven, 1907; member of the American Medical Association; served during World War I; died March 31, aged 68, of cerebral hemorrhage.

Henri Coutard, Colorado Springs, Colo.; Université de Paris Faculté de Médecine, France, 1902; one of the pioneers in research in radium and formerly director of x-ray therapy, Curie Institute, Paris, France; in 1937 joined the Chicago Tumor Institute serving until 1941 when he became chief of research, Glockner Penrose Hospital; known for his work on x-rays and a special method of treatment, the "Coutard method"; died in the LeMans Central Hospital in France March 16, aged 73, of cerebrovascular disease.

Henry Hallam Covell, Bernardsville, N. J.; Harvard Medical School, Boston, 1892; formerly practiced in Rochester, N. Y., where he was a member of the board of health and the Monroe County Milk Commission; died April 7, aged 87, of cerebral hemorrhage.

Robert Ronayne Culbert, Boston; University of Vermont College of Medicine, Burlington, 1891; formerly affiliated with St. Elizabeth Hospital and the Boston Dispensary; died March 23, aged 82, of heart disease.

✦ Indicates Fellow of the American Medical Association.

John Peter Denby, Carlinville, Ill.; Marion-Sims College of Medicine, St. Louis, 1898; served as president and treasurer of the Illinois Tuberculosis Association; president and director of the Farmers and Merchants Bank; died recently, aged 78, of heart disease.

DeWitt Clarence Dever, Seattle; Northwestern University Medical School, Chicago, 1928; member of the American Medical Association; died March 23, aged 52, of coronary heart disease and arteriosclerosis.

Homer Odell Dolley ✠ Bloomington, Ill.; Northwestern University Medical School, Chicago, 1929; member of the American Association of Industrial Physicians and Surgeons; past president of the McLean County Medical Society; on the courtesy staff of Brokaw Hospital in Normal; died March 25, aged 48, of coronary disease.

Paul Lowell Douglas, Pursglove, W. Va.; Washington University School of Medicine, St. Louis, 1939; member of the American Medical Association; served during World War II; died April 17, aged 40, as the result of bullet wounds alleged to have been inflicted by a former patient.

John Henry Duncan, Killbuck, Ohio; Ohio Medical University, Columbus, 1904; died in the Holmes County Joel E. Pomerene Memorial Hospital, Millersburg, March 11, aged 72, of injuries received in an automobile accident.

Eugene Harold Eising ✠ New York; Columbia University College of Physicians and Surgeons, New York, 1898; fellow of the American College of Surgeons; affiliated with Sloane Hospital for Women, Sydenham Hospital, Hospital of the Rockefeller Institute for Medical Research, Hospital for Joint Diseases and Mount Sinai Hospital, where he died March 29, aged 76, of heart disease.

Albert Henry Evans, Guilford, N. Y.; Syracuse University College of Medicine, 1902; member of the American Medical Association; past president of the Chenango County Medical Society; for many years served the town of Guilford as health officer and as a member of the school board; affiliated with Chenango Memorial Hospital, Norwich, where he died April 4, aged 76, of chronic congestive myocardial failure.

Arthur Louis Fehsenfeld, Trappe, Md.; University of Maryland School of Medicine, Baltimore, 1909; member of the American Medical Association; served on the staff of the Maryland General Hospital in Baltimore; died in the Cambridge-Maryland Hospital in Cambridge, March 31, aged 63, of myocardial failure.

H. Ward Fisher, Wilkes Barre, Pa.; Hahnemann Medical College and Hospital of Philadelphia, 1911; member of the American Medical Association; affiliated with the Wyoming Valley Homeopathic Hospital; died in Hahnemann Hospital, Philadelphia, March 14, aged 64, of uremia.

Desider Foldes ✠ Cleveland; Magyar Királyi Pázmány Petrus Tudományegyetem Orvosi Fakultasa, Budapest, Hungary, 1905; fellow of the American College of Surgeons; on the staff of St. John's Hospital, where he died March 27, aged 69, of carcinoma of the stomach.

Arthur Morris Gabriel ✠ New York; Vereinigten Friedrichs-Universität Medizinische Fakultät, Halle-Wittenberg, Prussia, Germany, 1923; affiliated with Metropolitan and Jewish Memorial hospitals; died April 23, aged 52, of acute infectious hepatitis.

Arnold William Garlitz, Dayton, Ohio; National University of Arts and Sciences Medical Department, St. Louis, 1913; affiliated with Veterans Administration hospitals at various places; died in the Veterans Administration Hospital March 30, aged 76, of posterior myocardial infarction.

Zeffa Carl Hagan, Union, Miss.; St. Louis College of Physicians and Surgeons, 1905; member of the American Medical Association; served during World War I; county health officer; affiliated with Laird's Hospital; died March 21, aged 70, of coronary occlusion.

Howard Cyrus Harper ✠ New Castle, Pa.; Jefferson Medical College of Philadelphia, 1904; past president of the Lawrence County Medical Society; veteran of the Spanish-American War and World War I; on the staff of Jameson Memorial Hospital; died March 6, aged 74, of cerebral hemorrhage and coronary heart disease.

Carl Floyd Hartmann ✠ Wauseon, Ohio; Rush Medical College, Chicago, 1909; past president of the Fulton County Medical Society; died in St. Vincent's Hospital, Toledo, April 18, aged 66, of coronary thrombosis.

William R. Haynie, Belton, S. C.; University of Nashville (Tenn.) Medical Department, 1896; member of the American Medical Association; died March 6, aged 79, of chronic nephritis.

William C. Heaston ✠ McPherson, Kan.; Ensworth Medical College, St. Joseph, Mo., 1908; fellow of the American College of Surgeons; past president of the McPherson County Medical Society; on the staff of McPherson County Hospital, where he died March 4, aged 77, of cerebral hemorrhage.

Edward Albert Herr ✠ Cheshire, Conn.; University of Vermont College of Medicine, Burlington, 1909; fellow of the American College of Surgeons; served during World War I; consulting gynecologist at St. Mary's Hospital in Waterbury, where he died March 18, aged 67, of coronary occlusion.

Clarence Payne Howley ✠ New York; Columbia University College of Physicians and Surgeons, New York, 1918; fellow of the American College of Surgeons; affiliated with Harlem Hospital and St. Vincent's Hospital; died April 3, aged 58, of acute coronary occlusion.

Fred T. Hughes, Gurdon, Ark. (licensed in Arkansas in 1903); died recently, aged 71.

Jacob Sleeper Kelley ✠ Providence, R. I.; Harvard Medical School, Boston, 1904; specialist certified by the American Board of Radiology; member of the New England Roentgen Ray Society and the Radiological Society of North America; served in France during World War I; until 1940 active in the Rhode Island National Guard; associated with the Charles V. Chapin, Roger Williams General and Providence Lying-In hospitals and the Veterans Administration hospital, where he died March 18, aged 70, of carcinoma.

Joseph Edward Knighton ✠ Shreveport, La.; University of Nashville (Tenn.) Medical Department, 1899; specialist certified by the American Board of Internal Medicine; fellow of the American College of Physicians; past president of the Louisiana State Medical Society; formerly vice president of the Southern Medical Association; for many years member of the state board of medical examiners; affiliated with the Tri-State Hospital; served on the staffs of the Shreveport Charity Hospital and the Pines Sanatorium; died March 9, aged 79.

Benjamin Franklin Kuhn, Pierceton, Ind.; Bennett Medical College, Chicago, 1897; member of the American Medical Association; died April 4, aged 81, of coronary thrombosis.

Kenneth Parker Lancefield, Portland, Ore.; University of Oregon Medical School, Portland, 1925; member of the American Medical Association; on the staff of the Portland Sanitarium and Hospital; died March 27, aged 54.

Peter J. Latz ✠ Chicago; Dunham Medical College, Chicago, 1896; Jenner Medical College, Chicago, 1899; affiliated with St. Elizabeth Hospital and Alexian Brothers Hospital, where he died April 14, aged 90, of arteriosclerosis.

Charles Joseph Leverty, Bridgeport, Conn.; University and Bellevue Hospital Medical College, New York, 1901; member of the American Medical Association; served during World War I; affiliated with St. Vincent's Hospital; died March 21, aged 72, of adenocarcinoma of the large bowel.

Rolla Ernest Little, East St. Louis, Ill.; St. Louis University School of Medicine, 1906; member of the American Medical Association; affiliated with Christian Welfare Hospital and St. Mary's Hospital, where he died April 1, aged 70, of coronary occlusion, cerebral sclerosis and osteoarthritis.

Josiah G. McDonald, Urich, Mo.; University Medical College of Kansas City, 1901; served during World War I; died March 31, aged 75, of coronary thrombosis.

Olga McNeile ✠ Los Angeles; Los Angeles Department of College of Medicine, University of California, 1910; formerly police surgeon; died April 2, aged 67.

Lora Larason Marriott, Newark, Ohio; Physio-Medical College of Indiana, Indianapolis, 1896; formerly county coroner; served during World War I; for many years affiliated with the Veterans Administration; died March 25, aged 80, of arteriosclerosis.

Alfred John Metscher, Enid, Okla.; Washington University School of Medicine, St. Louis, 1927; member of the American Medical Association; died March 14, aged 55, of coronary disease.

Lawrence Delano Miller ✠ Toledo, Ohio; Eclectic Medical Institute, Cincinnati, 1915; affiliated with Toledo State, Toledo and Flower hospitals; served during World War I; died March 18, aged 57.

William Theodore Moke, Pittsburgh; Western Pennsylvania Medical College, Pittsburgh, 1896; died in Western Pennsylvania Hospital April 4, aged 73.

Vernon Hurschel Musick ✦ Oklahoma City; Northwestern University Medical School, Chicago, 1927; assistant professor of medicine at the University of Oklahoma School of Medicine; fellow of the American College of Physicians; served during World War I; died March 26, aged 49, of coronary thrombosis.

Jesse D. Neel, Ecru, Miss.; (licensed in Mississippi in 1891); member of the American Medical Association; died March 10, aged 91.

Cyrus F. Newcomb, Champaign, Ill.; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1904; member of the American Medical Association; formerly secretary of the Champaign County Medical Society; served as vice president of the Illinois State Medical Society; health officer of Champaign-Urbana; affiliated with Burnham City Hospital, where he died April 4, aged 70, of heart disease.

John Quincy Newell, Oklahoma City; Barnes Medical College, St. Louis, 1897; formerly state senator, U. S. marshal for the western district and warden of the state penitentiary; died February 10, aged 77, of arteriosclerotic heart disease.

Andrew Walsh O'Malley, Clarks Summit, Pa.; Illinois Medical College, Chicago, 1908; member of the American Medical Association and the American Psychiatric Association; clinical director of Clarks Summit State Hospital; died March 11, aged 66, of coronary occlusion.

Bennett Roland Parker ✦ Chicago; Rush Medical College, Chicago, 1916; fellow of the American College of Surgeons; affiliated with Illinois Central Hospital; served during World War I; entered the Mayo Foundation in Rochester, Minn., as a fellow in surgery in October 1919 and left in April 1926; died April 15, aged 61.

Florence Pettus, New York; Washington University School of Medicine, St. Louis, 1936; member of the American Medical Association; affiliated with Roosevelt Hospital; died April 3, aged 40, of third degree burns and suffocation as the result of a fire of undetermined origin in her apartment.

John Linton Phythian, Newport, Ky.; Kentucky School of Medicine, Louisville, 1891; member of the American Medical Association; fellow the American College of Surgeons; president of the board of trustees of Speers Memorial Hospital, Dayton, where he died April 3, aged 80, of arteriosclerotic heart disease.

John Ransom Plank ✦ Steelton, Pa.; Jefferson Medical College of Philadelphia, 1896; school physician; died April 1, aged 82, of coronary thrombosis.

Frank Kenneth Pomeroy, Fresno, Calif; Columbia University College of Physicians and Surgeons, New York, 1914; member of the American Medical Association; served during World War I; regimental surgeon in the 185th Infantry of the California National Guard for many years; formerly member of the city board of health; on the staff of St. Agnes' and Community hospitals; died April 1, aged 64, of coronary thrombosis.

William Roy Richards ✦ Calhoun, Ga.; Atlanta School of Medicine, 1913; member of the American Medical Association; twice mayor of Calhoun; at one time member of the city council; served during World War I; formerly health commissioner of Greene County in Greensboro; died in the Veterans Administration Hospital, Atlanta, March 23, aged 59.

Luther Eldridge Roper, Hollywood, Fla.; Atlanta Medical College, 1893; died in Broward General Hospital, Fort Lauderdale, March 15, aged 79, of cardiac decompensation.

Donald Gordon Russell, Seattle; Queen's University Faculty of Medicine, Kingston, Ontario, Canada, 1885; died April 1, aged 87.

Henry Richard Schreiber ✦ Washington, D. C.; Georgetown University School of Medicine, Washington, 1907; professor of clinical medicine at his alma mater; past president of the Medical Society of the District of Columbia; on the staff of Providence Hospital; died April 9, aged 65, of coronary occlusion.

William Thomas Shipe, Middletown, Ohio; Baltimore Medical College, 1894; served during World War I; died in the Veterans Administration Hospital, Augusta, March 13, aged 83, of pulmonary edema, cerebral vascular accident and arteriosclerosis.

John Charles Siggins, North Hills, Pa.; University of Pennsylvania Department of Medicine, Philadelphia, 1901; served during World War I; formerly on the staffs of Philadelphia General and Wills Eye hospitals in Philadelphia; until his retirement chief oculist with the Pennsylvania Railroad; died March 29, aged 70, of suffocation as the result of a fire in the Belle Vista Sanatorium in Philadelphia.

Grace Stevens, Northampton, Mass.; Boston University School of Medicine, 1901; affiliated with the Cooley Dickinson Hospital, where she died March 20, aged 81, of coronary thrombosis.

James Albert Stone, Little River, S. C.; University of Maryland School of Medicine, Baltimore, 1905; died March 24, aged 71, of cerebral hemorrhage.

Joseph John T. Sweeney, Toledo, Ohio; Jefferson Medical College of Philadelphia, 1911; member of the American Medical Association; affiliated with Mercy Hospital and St. Vincent's Hospital, where he died March 16, aged 65.

Vincent Michael Timm, Metropolis, Ill.; Chicago Medical School, 1937; member of the American Medical Association; died recently, aged 50, of gastric ulcer and hemorrhage.

Frank Paige Todd, Danielson, Conn.; Boston University School of Medicine, 1889; member of the American Medical Association; served during World War I; in 1948 the Danielson Chamber of Commerce gave him its first annual Civic Achievement Award because he had served the community for more than a half century as a country doctor; formerly affiliated with the Day Kimball Hospital in Putnam; died March 15, aged 86, of angina pectoris.

John Walker, Lynchburg, Va.; University of Maryland School of Medicine, Baltimore, 1891; member of the American Medical Association; for many years surgeon for the Chesapeake and Ohio Railway; served on the staff of the Memorial Hospital, where he died March 27, aged 82.

Bernard Weiss, Boston; Tufts College Medical School, Boston, 1916; member of the American Medical Association; died in Peter Bent Brigham Hospital, Boston, March 27, aged 62, of coronary thrombosis.

Joseph Earl Wharton, Santa Ana, Calif.; Ohio State University College of Medicine, Columbus, 1940; member of the American Medical Association; served overseas during World War II; on the staff of St. Joseph Hospital in Orange; died in Los Angeles April 4, aged 35, of fracture of the femur with complications.

Lewis Butler Whiting, Baltimore; Johns Hopkins University School of Medicine, Baltimore, 1934; member of the American Medical Association; died January 26, aged 44.

Thomas Robert Whitmarsh, Stephenson, Mich.; Michigan College of Medicine and Surgery, Detroit, 1897; specialist certified by the American Board of Otolaryngology; fellow of the American College of Surgeons; served during World War I; died in the Veterans Administration Hospital, Woods, March 26, aged 77, of gangrene of the right lower extremity.

Arthur Farrington Wilhelm, Raubsville, Pa.; Medico-Chirurgical College of Philadelphia, 1909; died April 8, aged 71, of heart disease.

Gerard Thomas Willke ✦ Cincinnati; University of Cincinnati College of Medicine, 1921; affiliated with Deaconess Hospital, St. Mary Hospital and the Good Samaritan Hospital, where he died April 3, aged 53.

Leo Joseph Wojczynski ✦ Philadelphia; Jefferson Medical College of Philadelphia, 1911; affiliated with St. Mary's and Nazareth hospitals; died April 18, aged 63.

Clifford Harvey Wood, Glendora, Calif.; University of Southern California College of Medicine, Los Angeles, 1905; member of the American Medical Association; served on the staff of the Pomona Valley Community Hospital in Pomona; died March 30, aged 70.

William Hagood Woods, Myrtle Beach, S. C.; University of Nashville (Tenn.) Medical Department, 1905; member of the American Medical Association; died March 31, aged 69.

Stanley Worden ✦ Dover, Del.; Johns Hopkins University School of Medicine, Baltimore, 1926; formerly secretary of the Delaware State Board of Health; on the staff of Kent General Hospital; died in Pittsburgh April 11, aged 54, of coronary occlusion.

Harold Edson Wright ✦ Baltimore; University of Maryland School of Medicine and College of Physicians and Surgeons, Baltimore, 1919; specialist certified by the American Board of Radiology; member of the American Gastro-Enterological Association, Radiological Society of North America and the American College of Radiology; fellow of the American College of Physicians; affiliated with the South Baltimore General Hospital; died January 16, aged 56.

John Charles Zuercher ✦ Milwaukee; St. Louis University School of Medicine, 1912; died in the Mayo Clinic, Rochester, Minn., March 16, aged 64, of carcinoma.

Foreign Letters

ITALY

(From a Regular Correspondent)

FLORENCE, March 20, 1950.

Congress of Obstetrics and Gynecology

The fortieth National Congress of the Italian Society of Obstetrics and Gynecology was held at the University of Palermo, in Sicily. The chairman of the organization committee was Prof. Salvatore Scaglione, director of the university clinic. The congress was attended by the directors of almost all Italian university clinics and by numerous specialists from Italian hospitals. Also present were some professors of the medical faculties of Paris and Vienna.

Prof. Giovanni Paroli of Perugia presented a report on conduct of labor with regard to kinetics of the uterus.

Considering the uterus as being divided in two segments, the upper and the lower, which are equipped with different neuromotor systems, he believes that, in the light of modern knowledge, the adrenergic system would be substantially the motor of the upper segment and the inhibitor of the lower segment, while the cholinergic system would be the inhibitor of the upper segment and the motor of the lower one. The uterine muscular cell would be provided with both specific receptors, with prevalence of the adrenergic in the upper segment and the cholinergic in the lower one. During pregnancy the upper segment is in a state of tonic adaptation, while during labor contractions take place. These contractions have an ascending curve intermittently broken by intervals of almost horizontal direction. During these intervals, however, the uterus does not return to the state of tonic adaptation but remains in a state of basal contraction between the two phases. Inverting the terms, the same may be said of the lower segment.

Among the intrinsic factors which may influence the kinetics of the uterus, the estrogens are acting in an excitomotory sense and the luteinic hormones exert an inhibitory action, while the action of histamine still remains obscure. The extrinsic factors which influence uterine contractions may have either a stimulating or an inhibitory action. Among those with stimulating action are the ergot derivatives, sparteine sulfate, some digitalis derivatives and quinine in small doses. Sodium beta-glycerophosphate is first in order among the factors with an inhibitory action on uterine contractions.

With regard to the kinetics of the uterus, primary inertia originates from abnormal or insufficient development of the uterus or from a deficiency of the necessary elements for a normal establishment of the contractions. Therapy should therefore be directed particularly to increase the excitability of the muscular elements through the use of estrogens, small quantities of quinine, posterior pituitary hormone and derivatives of ergot. The secondary inertia results principally from muscular fatigue combined with psychic inhibition and hyperalgesia. Therapy should consist principally in restoring muscle energy by administration of dextrose, insulin, thiamine hydrochloride and ascorbic acid according to individual needs. For hyperkinesia of the upper segment the administration of sympathicolytic drugs is useful, while for hyperkinesia of the lower segment therapy should consist principally of parasympathicolytic drugs, the local application of which may be preferred. The condition of total spasticity of the uterus should be treated by ample administration of muscular sedatives.

Analgesia in Labor

Before Professor Scaglione discussed the second subject, a legislative proposal was discussed in the presence of Professor Cotellesa, High Commissioner of Hygiene and Public Health. This law would provide for the training of obstetricians in the administration of analgesics to parturient women and for obstetric clinics to be provided with analgesic equipment and would establish the right of women in confinement (in obstetric clinics) to request analgesia. This law, if approved by the Parliament, would constitute an innovation in Italy.

Professor Scaglione recalled that in 1939 the Italian Society of Obstetrics and Gynecology dealt with the subject of painless childbirth; Professor Dallera presented a report and recommended caution in the use of barbiturates while advocating inhalation of nitrous oxide and parenteral administration of morphine derivatives. In 1948 the Academy of Sciences of Udine was concerned with this subject, and the speaker, Debiasi, concluded that all methods known at present were unsatisfactory.

In a recent publication, Repetti concluded, from his experience in the use of many drugs, that during the period of expulsion the use of nitrous oxide, cyclopropane and trichlorethylene is excellent, but that these anesthetics require constant supervision by the physician. According to Repetti none of the methods is perfect for analgesia for the entire duration of labor.

Professor Scaglione surveyed the American literature on the subject, recalling that analgesia during childbirth is accomplished particularly with cyclopropane and ethyl ether while there is a tendency to abandon chloroform and nitrous oxide. Vinyl ether is not much used. Trichloroethylene does not always have an analgesic response and may produce postpartum hemorrhage. He stated that there is at present no ideal method for rendering childbirth painless and that inhalation is at present the most practical method but that it must always be entrusted to a physician.

Gynecologic Physiopathology

Professor Martinolli discussed the gynecologic physiopathology in all the successive phases of development until puberty. He began with a review of the anatomic knowledge concerning the development of the sex organs, the pelvis and the mammary glands during the prenatal period. He discussed also the postnatal phenomena known as the genital crisis of the newborn. The speaker stressed functional anomalies of the genitalia, such as sexual precocity, premature puberty and the genital diseases of disturbed development. Of particular intricacy is the problem of prepuberal pathology of traumatic origin. The speaker stressed that the practitioner should abandon the concept that the female genitalia do not require attention before puberty and he should not treat disturbances related to the genital region without making a gynecologic examination.

DENMARK

(From a Special Correspondent)

COPENHAGEN, April 23, 1950.

A Salt-Free Diet for Heart Disease

The treatment of heart disease with a salt-free diet dates back many years. But a study of the subject by Dr. A. Levin Nielsen, Dr. P. Bechgaard and Dr. H. O. Bang published in the *Journal of the Danish Medical Association* suggests that this treatment has not been used enough. In the past many Danish hospitals have been satisfied with a diet containing at least 3 Gm. of sodium chloride daily. Now an attempt has been made to reduce this amount to less than 1 Gm. daily, a diet which of course requires the services of a skilled dietitian. Sixty-four patients were selected for this apparently rather heroic treatment. Their ages ranged from 40 to 84, the average age being 62. All presented signs of cardiac insufficiency, with edema and/or cyanosis, congestion of the lungs (with roentgenographically verified pulmonary stasis) and attacks of dyspnea and edema of the lungs. In 4 of the worst cases an attempt was first made in hospital to treat with such standard remedies as rest in bed, digitalis and diuretics. It was only after they had failed that the salt-free diet was instituted. The results in these 4 cases are described as "almost dramatic" after only a few days.

Although many of the patients complained of the monotony of the diet, none showed signs of salt deficiency as indicated by lassitude and weakness. The most impressive response to this treatment was made by a woman, aged 64, who lost 27.6 Kg. in two months. The patients were followed for three to 18 months after discharge from hospital, and those who had kept to a salt-free diet after discharge were compared with those who had not done so. Among 31 who had adhered to this diet there were 27 who were as fit as they had been on discharge. One was worse, and 3 had died. Among the 19 who had not adhered to their diet there were 3 who were as well as they had been on discharge, 11 were worse and 5 had died. This evidence is not convincing statistically, but the detailed account given of the 4 most serious cases is interesting.

Epidemic Diseases in 1949

The official figures for the incidence of epidemic diseases in Denmark in 1949 are now published; they are alternately encouraging and depressing. The figures for typhoid and paratyphoid B are 19 and 83, respectively, and are encouraging when compared with the previous 40 and 120, respectively. But the 148 cases of epidemic cerebrospinal meningitis are discouraging when compared with the prewar 65. The same may be said of acute anterior poliomyelitis with paralysis, 155 as compared with 50. Scarlet fever showed little change from the "calculated normal," the figures being 9,458 and 9,200, respectively. But diphtheria seems to be receding, there being only 84 cases as compared with 1,350. This is surely due to a well organized campaign against diphtheria.

The figures for the venereal diseases are not cheering, though congenital syphilis shows a fall, 32 as compared with 40. But acquired syphilis was reported in 1,032 cases, as compared with only 515, and gonorrhea in 11,063 cases, as compared with 8,250. Evidently there has not been complete recovery from the wartime wave of venereal disease. The incidence of bronchopneumonia was high, with 46,422 cases as compared with 22,500, as was that of croupous pneumonia, with 6,935 cases as compared with 3,700. Acute epidemic hepatitis showed a rise, 8,256 as compared with 2,800. Rheumatic fever showed little change from the "calculated normal."

Tuberculin Studies

In 1932 Dr. Thorvald Madsen, then head of the Serum Institute in Copenhagen, instituted a series of far reaching epidemiologic studies of tuberculosis in Denmark. These studies, supported by the Rockefeller Foundation, have consisted largely of tuberculin testing. Previously it had generally been assumed that it was superfluous to repeat tuberculin tests on persons found to be tuberculin-positive, for this condition was held to be permanent. But in 1934 the decision was made to test positive reactors among school children repeatedly. Between 1934 and 1936 Dr. Per Helweg-Larsen was attached to the Serum Institute, and he has continued his studies of tuberculosis ever since.

Dr. Helweg-Larsen's latest study, published as a 138 page volume by Rosenkilde and Bagge of Copenhagen in 1950, deals with three medium-sized provincial towns in a part of Denmark which is now free from bovine tuberculosis. Special attention was paid to the persons contracting a primary tuberculous infection, whether they were between the ages of 7 and 14 or 15 and 34. Another group consisted of 84 medical students between the ages of 18 and 29. At first several different tuberculin tests were employed, but eventually the Pirquet and Moro tests were abandoned, and only the intracutaneous Mantoux test was employed. Among 465 school children who had become tuberculin-positive one to three years earlier, there were as many as 36 (7.7 per cent) who again became tuberculin negative. Such reversion was most frequent among the children whose original positive reaction to tuberculin had been slight. Some of these reversions may be explained as the result of a faulty interpretation of the tuberculin reactions, but in most cases reversion had actually taken place in the opinion of Dr. Helweg-Larsen, who discusses at some length the implications of this curious phenomenon. He has been awarded the M.D. degree for this study.

Campaign Against Dental Disease

The large Danish island of Bornholm has since 1937 been the scene of a well organized campaign against dental disease. Reporting on this activity in the *Journal of the Danish Medical Association*, Dr. H. C. Olsen divides his material, consisting of more than 22,000 observations, into two five year periods, 1937-1941 and 1942-1946. Broadly speaking, these were prewar and war periods, respectively. Between these two periods the caries-free teeth of school children rose from 7.2 to 11.3 per cent. In the period under review growing attention has been paid to school dentistry and to the provision of cod liver oil in the winter months. The war reduced the supplies of margarine, coffee, sugar, white bread and cakes and promoted the consumption of butter, milk and rye bread. One of Dr. Olsen's most curious observations is that the percentage of underweight school children (10 per cent under normal weight) actually fell during most of the war years. Since then this percentage has risen, and in 1948-1949 it was 14.6, as compared with only 9.4 in 1943-1944.

AUSTRALIA

(From a Regular Correspondent)

BRISBANE, April 26, 1950.

Crisis in Blood Transfusion Services

In 1946, the Australian Red Cross Society embarked on a countrywide blood transfusion service as part of its peace time program. Until that time, blood transfusion had not been developed on a national basis, although many large hospitals and some doctors had established transfusion services.

Prior to 1939 the Red Cross had established donor panels, from which donors could be directed to hospitals that needed blood. A few blood banks had been established on a limited basis.

The stimulus of war demands in the Southwest Pacific increased the tempo of blood and serum transfusion, and Red Cross donor panels were developed to meet this demand. The responsibility for taking and processing of the blood was, however, assumed by the army, which established special medical units for the purpose. These operated in the principal cities and, later, the forward base areas. This year, Australia's monthly usage of blood and serum approximates 2,650 liters of blood and 700 liters of serum. The serum is processed by Red Cross in New South Wales, Queensland and Western Australia. Blood received from Red Cross in Victoria, South Australia and Tasmania is processed by the Commonwealth Serum Laboratories in Melbourne, which will, in the future, also fractionate the serum. There has been, so far, a low incidence of homologous serum jaundice, and protein hydrolysates have not been widely used.

The blood and serum is supplied free of cost to anyone in Australia requiring it, and no service charge is made to cover these costs. One result of this is that the expenditure on all Red Cross activities (to service and exservice personnel, convalescent homes, blood transfusion, antituberculosis work, handcrafts and libraries, Junior Red Cross, transport and overseas relief) for the year ended June 1949 was nearly £900,000 ($2,000,000) and the total receipts (including government subsidies) only £500,000 ($1,110,000). Of these costs the blood

transfusion services represented one of the largest expenditures. Almost all the Red Cross personnel engaged in the transfusion service are salaried, and the unit costs are more than double those of another transfusion service in Australia.

For the past four years the Red Cross has financed its peace time program with the help of the large surplus carried over from its war time appeals, but the present services cannot be maintained with the income available. It would seem that the virtual monopoly of blood transfusion services on a national scale free of cost to the user is beyond the willingness of the people to support. This is in spite of phenomenal export prices for primary products. The more extended use of blood and blood products will only further complicate the position. Further increase of government subsidies would develop prejudice by the medical profession, who are strenuously opposing the nationalization of medical services.

ARGENTINA

(From a Regular Correspondent)

BUENOS AIRES, April 26, 1950.

New Plan for Medical Studies

A new plan for medical studies has been established this year in the medical school of the University of Buenos Aires. The course will require seven years for completion, each academic year extending from March 15 to November 15, with a holiday of 15 days. The plan provides: first year anatomy, histology and embryology; second year, physiology, biochemistry and biophysics; third year, pathology, surgical technic, pharmacology, bacteriology and parasitology; fourth year, symptomatology, surgical pathology and radiology; fifth year, internal medicine, surgery, pediatrics, infectious diseases, hygiene, psychiatry, neurology, dermatosyphilography, ophthalmology and otorhinolaryngology; sixth year, internal medicine, nutrition, surgery, obstetrics, forensic medicine, toxicology, gynecology and urology, and seventh year, after approving examinations in internal medicine every student will attend for three months each a department of medicine, a surgical department and an obstetric service. Orthopedics, traumatology and phthisiology have been transferred from the ordinary curriculum to the postgraduate school.

In theory, each student should attend in the first year, 6 hours of theoretical classes and 15 hours of practical exercises per week and 7 and 17 hours, respectively, in the second year. But, because of the large number in each year, the students have to attend the classes in groups and can do practical work only once each week or two.

In South American medical schools, examinations are more important than practical work. Students try to learn only what professors ask for in the examinations and they read special books which may not be the best, in order to be able to answer the questions.

Recently the dean of the medical school of Buenos Aires announced a completely new rule: from now on there will be examinations every month of the school year. Those who do not pass one examination can be examined again within 60 days (in the same subject); i. e., they have opportunity of being examined three times a year. While they are studying one subject for these periodic examinations, they can attend the practical work of the following year, although they have no time for the study of the subject in which they are doing practical work.

When the students take part in the government of the universities, as frequently occurs in South America, the usual request of the students is for more examinations. Granting of this request is the best way of winning votes in these schools, where the votes of the students are important for nomination of the members of the councils of the university schools.

American Congress of Obstetrics and Gynecology

A large delegation of outstanding Argentine physicians will attend the American Congress of Obstetrics and Gynecology, which will be held in New York, May 14-19. Dr. J. A. Salaber, president of the Argentine Society of Obstetrics and Gynecology; Dr. J. León, vice president; Dr. A. Peralta Ramos Jr., secretary; Dr. G. di Paola, treasurer; Dr. J. C. Ahumada, professor of gynecology and author of a textbook on gynecology; Dr. M. L. Perez, professor of obstetrics and author of a textbook on obstetrics (both these books are widely used in the medical schools of Latin America), and Drs. F. Merchante, R. Chevalier, J. Mezzadra and D. Nolting form this delegation. Almost all the members of this group have been in Europe, but for more than half of them this will be the first visit to the United States. Many of them have completed their training in France or in Germany.

Gynecology is well developed in Argentina, especially with regard to pathologic anatomy and surgical technics. In the official chair of the Faculty of Medicine the studies have been specially directed toward cancer in women. Original research on physiology and endocrinology have not reached the same high level. Probably this visit to the United States will greatly aid a better understanding and encourage exchange of knowledge between North American and Argentine specialists in gynecology and obstetrics.

BRAZIL

(From a Regular Correspondent)

RIO DE JANEIRO, April 28, 1950.

New Outlook for BCG Immunization

As head of the BCG department of the Ataulpho de Paiva Foundation, an institution which cooperates with the Rio de Janeiro Department of Health in the work of immunization of the infants against tuberculosis, Dr. Arlindo de Assis has had much experience in the preparation and use of the immunizing material. After importing the original BCG from France in 1927, he began to introduce some changes in the preparation of the vaccine and some improvements in the immunization technic, mainly by increasing the doses, at the same time making experimental studies on tuberculin allergy. Dr. Assis has recently prepared a critical study on the whole problem, summarizing his experience as well as that of Nascimento, Alvim, Fernandes, Silveira, Rosemberg and Carvalho in "New Perspectives of BCG Immunization."

He states that the various methods of immunizing man with BCG used until now have proved, as a rule, capable of giving some protection against morbidity and mortality from tuberculosis. Owing to the different technics used for this immunization throughout the world and the various criteria adopted for ascertaining the degree of specific protection given by BCG, the author believes that the present results of BCG vaccination represent only the minimum of its potential benefits. Comparison of BCG immunization against tuberculosis with the vaccinations against other transmissible diseases proves that, from the standpoint of the immunologic technic as well as from the public health significance, the former must be considered the least developed. The application of BCG vaccination in various countries, as an efficient weapon for the fight against tuberculosis, needs, besides attention to doctrinal principles common to all, examination of the infectious as well as the socioeconomic components which guide the epidemiology of tuberculosis in each country. The choice of the method for the BCG immunization must be adapted to the local conditions of production, application and control of the specific protection against the forms of

tuberculous primary infection and reinfection, in accordance with a plan of progressive work and with the general result which will be obtained through the years.

The experience accumulated in Brazil for more than twenty-two years proves that the oral administration of BCG, when correctly executed, may be able to confer strong protection against the severe forms of child tuberculosis prevalent in this country. Oral immunization with large doses of BCG, repeated monthly during the first six months of life of children exposed to tuberculosis (concurrent vaccination) has resulted, in the last four years, in a decrease of tuberculosis mortality to zero and has reduced the tuberculosis morbidity to 15 per cent among those with roentgen indications of tuberculosis. Observation of more than 400 children subjected to this concurrent vaccination shows evidence of control of the infectious component of tuberculosis epidemiology never before attained with conventional methods of fighting the disease. The use of large oral doses of BCG in tuberculin-positive children and adults was demonstrated to be completely harmless. BCG immunization of more than 300 allergic persons of various ages, since 1946, is beginning to show an inhibiting effect on progressive tuberculosis, as now demonstrated through the reduction of the specific morbidity. At the same time, this immunization has demonstrated a desensitizing effect on the tuberculin allergy caused by natural infection.

These observations prove that BCG vaccination can be applied, as a general measure, to all persons who are free from progressive tuberculosis but who are exposed to active sources of infection.

Chest Survey of School Children and Teachers

During 1949, the Division of School Health of the Rio de Janeiro Department of Education performed a miniature roentgenographic chest survey of a large sample of school children. Of the 35,689 children examined, 340 (0.95 per cent) showed signs of abnormal forms and intensities of shadows. In 192 (0.54 per cent) there were pulmonary abnormalities and in 148 (0.41 per cent) cardiovascular abnormalities. The 340 children were subjected to standard teleradiographic and clinical examination, the results of which have not yet been made public. At the same time, 1,357 teachers were examined; 51 (3.02 per cent) showed pulmonary abnormalities. These figures are not much different from those previously reported by M. de Abreu, A. de Paula and Benedetti, who were pioneers in the use of miniature roentgenograms as a screen test for pulmonary tuberculosis.

An interesting finding of the survey was the exceedingly high rate of cardiovascular abnormalities among teachers: 258 (19.01 per cent) showed such changes, which are being further investigated.

Chronic Myocarditis in American Trypanosomiasis

Dr. R. Chiaverini, assistant professor of medicine at the São Paulo University, published a report on 39 patients with chronic Chagas' disease (American trypanosomiasis), aged 20 to 59 years and all presenting specific myocarditis. The initial symptoms of cardiac trouble were registered in 35 cases, most of the patients experiencing effort dyspnea, edema and palpitation. On the entry to the hospital, the most prominent cardiac symptoms were those of left ventricular failure. The physical examination demonstrated an anomalous seat of the heart beat, great frequency of systolic murmur at the mitral focus with dulness of both sounds, normal or low blood pressure, increased venous pressure and circulatory velocity. Signs of stasis were present in the lungs of 74.3 per cent of the patients and enlarged liver in 84.6 per cent. Roentgenographic examination in 29 cases showed an enlarged heart, especially in the left ventricle, in 27. The electrocardiographic examination of 37 patients demonstrated troubles of the excitoconductor system, 51.3 per cent of ventricular extrasystoles and great frequency of block, mainly of the right bundle (40.5 per cent). Left branch block was present in 10.8 per cent of cases, auriculoventricular partial block of first degree in 5.4 per cent and arborization block in 2.7 per cent. Other changes of the QRS segment were present in 27.0 per cent, changes of the T wave in 16.6 per cent, auricular fibrillation in 5.4 per cent, auricular flutter in 2.7 per cent and a curve of left ventricular hypertrophy in 2.7 per cent. The fatality rate was high (12 cases, or 31.7 per cent), the deaths being more frequent in patients under 40 years of age.

Cancer in Gynecologic Patients

The third periodical report of cases of cancer of the cervix treated at the Gynecological Institute of the Rio de Janeiro University, under the direction of Dr. Arnaldo de Moraes, announces decided progress in early cancer detection through routine colposcopy, vaginal smear and, in cases of myoma, previous curettage of the uterus, with histologic examination of the mucosa thus obtained. Of 4,747 patients, 379 (7.99 per cent) had cancer of the cervix or of the cervical canal, six of which were microcarcinomas. Of this 379 cases, 6 were cancer in situ, 25 of grade I, 57 of grade II, 227 of grade III and 64 of grade IV. Surgical intervention was the main form of treatment in 51 cases, the operations being as follows: amputation of the cervix 1, abdominal total hysterectomy 3, Wertheim's operation 28 and Schauta's operation 17. Curietherapy and roentgen therapy, alone or associated with operation, were used in 217 and 198 cases, respectively. Symptomatic treatment was applied in 67 cases. Eighty-seven deaths were registered as follows: 19 during the symptomatic treatment, 9 from local relapse after operation, 16 from relapse and cachexia after curietherapy (one to five years after treatment), 20 from relapse or persistence of cancer after curietherapy plus roentgentherapy, 5 during the postoperative period, 7 after curietherapy and 11 during palliative roentgen therapy. Of the 379 cases of cancer of the cervix, 12 were of cancer of the cervical stump, discovered six months to 34 years after supravaginal hysterectomy (5 cases of epidermoid carcinoma, 1 case of adenocarcinoma, 2 cases of globocellular sarcoma and 4 cases without histologic diagnosis).

Central Nervous System Lesions in Brazilian Blastomycosis

In a series of 11 examinations performed on the cadavers of persons who died of Lutz's disease, or Brazilian blastomycosis (paracoccidioidomycosis), by Dr. A. Penna de Azevedo, of the Oswaldo Cruz Institute, in 3 cases, besides the involvement of different organs and tissues, extensive and severe lesions of the central nervous system (cerebrum, cerebellum, pons and meninges) were seen. Lesions of Brazilian blastomycosis in the central nervous system are rare, and, according to the author, no other cases have been described in which the lesions involved the nervous tissue itself. In this series, the incidence was 81.8 per cent in the lungs and 18.1 per cent in the intestines. In 2 of the cases there were nodules as large as a hazelnut, in the substance of the cerebrum, cerebellum and pons. Histologic examination showed the characteristic inflammatory lesion with granulomas and parasites in abundance, not only in the giant cells but in the rest of the tissue. Often the parasite was shown only by its capsule, giving the tissue a vacuolated or sievelike appearance. In 1 case the lesion involved only the meninges after extensive involvement of the scalp and bones of the cranium and lumbar vertebrae. In this case also the presence of the parasite was easily proved. The parasite isolated in all 3 cases was always the Paracoccidioides (Blastomyces) brasiliensis.

Correspondence

APPETITE AND OLFACTORY ACUITY

To the Editor:—You have recently commented editorially (**142**:1080 [April 8] 1950) on the interesting reports of F. R. Goetzl and his colleagues, describing a relation between appetite and olfactory acuity. It may not be amiss therefore to point out that an independent attempt to verify the existence of this relation has been completely unsuccessful. In the course of a systematic study of the factors regulating food intake in men and animals, both olfactory and taste sense acuity were studied (*J. Applied Physiol.* **2**:217, 1949). Only minor fluctuations were observed in the acuity of these senses throughout the day, and these bore no consistent relation to the presence or absence of hunger sensations and appetite (the desire to eat). The abolition of appetite by a synthetic drug was also not related to changes in the acuity of the gusto-olfactory senses.

The reliability of the methods for testing both senses is high, and the tests give excellently reproducible results, so that we cannot attribute our failure to confirm Goetzl's observations to technical unreliability or masking by random fluctuations. Unfortunately, the mechanisms by which tissue needs regulate food intake, and their disturbances in disease, are as yet almost completely unknown.

HENRY D. JANOWITZ, M.D.,
Mount Sinai Hospital, New York.
M. I. GROSSMAN, M.D.,
University of Illinois Medical College, Chicago.

LOSS OF IRON THROUGH THE SKIN

To the Editor:—In your editorial "Recent Studies of Iron" (page 904, March 25, 1950) you called attention to large losses of iron in the sweat as reported by Mitchell and Hamilton (*J. Biol. Chem.* **178**: 345, 1949). We have recently studied the iron content of sweat obtained from 25 normal persons (Adams, Leslie and Levin: Dermal Loss of Iron, to be published, *Proc. Soc. Exper. Biol. & Med.*) with special attention to cellular as against noncellular components. After centrifugation we found the supernatant to be clear and free of epithelial cells. This liquid was found to be virtually free of iron. On the other hand, opalescent, uncentrifuged sweat was found to have a high content of iron. These findings lead us to the belief that the dermal loss of iron is not a function of sweating but is the result of desquamation.

WILLIAM S. ADAMS, M.D.
ALAN LESLIE, M.D.
MELVIN H. LEVIN, M.D.
Veterans Administration Center
Research Service, Los Angeles.

DR. MAURICE I. SMITH

To the Editor:—In noting the retirement of Dr. Maurice I. Smith as the chief pharmacologist of the Public Health Service in THE JOURNAL, April 22, I am reminded of his great contribution to the solution of the problem of the etiology of "ginger paralysis" twenty years ago this spring. This form of paralysis affected a relatively large proportion of the population throughout some of the midwestern and southwestern states with great rapidity. It was soon discovered that the disease was closely associated with the drinking of an adulterated fluid extract of ginger, and it was Dr. Smith and his co-workers who promptly disclosed the fact that the paralysis was due to triorthocresyl phosphate. The incidence of the disease was immediately affected by this discovery, and only a few cases occurred after 1931. The work of Dr. Smith and his colleagues was of the highest character and deserves particular mention at this time, in view of his thirty years of research at the National Institute of Health and its predecessor, the Hygienic Laboratory.

HENRY R. VIETS, M.D., Boston.

Medical Examinations and Licensure

COMING EXAMINATIONS AND MEETINGS

NATIONAL BOARD OF MEDICAL EXAMINERS

NATIONAL BOARD OF MEDICAL EXAMINERS: *Parts I and II.* Various locations, June 19-21. *Part III.* Twenty-nine centers, June 6-29. Registration closes on May 6. Exec. Sec., Mr. E. S. Elwood, 225 S. 15th Street, Philadelphia.

EXAMINING BOARDS IN SPECIALTIES

AMERICAN BOARD OF ANESTHESIOLOGY: *Written.* Various locations, July 21. *Oral.* Chicago, Oct. 8-11. Sec., Dr. Curtiss B. Hickcox, 745 Fifth Ave., New York 22.

AMERICAN BOARD OF INTERNAL MEDICINE: *Oral.* San Francisco, June 21-23. The oral examinations in the subspecialties will be held at the same time and places. *Written.* Oct. 16. Asst. Sec., Dr. William A. Werrell, 1 West Main Street, Madison 3, Wis.

AMERICAN BOARD OF NEUROLOGICAL SURGERY: *Oral.* Chicago, June 3. Applications no longer accepted. Chicago, Oct. 1950. Final date for filing applications is April 30. Sec., Dr. W. J. German, 789 Howard Ave., New Haven, Conn.

AMERICAN BOARD OF OPHTHALMOLOGY: *Written.* Various Centers, January 1951. Final date for filing applications is July 1, 1950. Chicago, Oct. 2-6; West Coast, Jan. 1951. Sec., Dr. Edwin B. Dunphy, 56 Ivie Road, Cape Cottage, Maine.

AMERICAN BOARD OF OTOLARYNGOLOGY: Chicago, October. Sec., Dr. Dean M. Lierle, University Hospital, Iowa City.

AMERICAN BOARD OF PATHOLOGY: St. Louis, Oct. 13-14. Sec., Dr. Robert R. Moore, 507 Euclid Ave., St. Louis 10.

AMRICAN BOARD OF PEDIATRICS: San Francisco, June 30-July 2. Exec. Sec., Dr. John McK. Mitchell, 6 Cushman Road, Rosemont, Pa.

AMERICAN BOARD OF PHYSICAL MEDICINE AND REHABILITATION: *Oral and Written.* Boston, Aug. 26-27. Final date for filing applications is April 1. Sec., Dr. Robert L. Bennett, 30 N. Michigan Ave., Chicago.

AMEDICAN BOARD OF PLASTIC SURGERY: *Oral.* May-June. Sec., Dr. Louis T. Byars, 4647 Pershing Avenue, St. Louis, Mo.

AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY: San Francisco, June 23-24. Applications no longer accepted. Next examination, December 1950. Final date for filing applications is Sept. 1.

AMERICAN BOARD OF RADIOLOGY: *Oral.* Chicago, week of June 18. Sec., Dr. B. R. Kirklin, 102-1210 Second Ave., S.W., Rochester, Minn.

AMERICAN BOARD OF SURGERY: *Written.* Various centers, Oct. 25. Final date for filing applications is July 1. Sec., Dr. J. Stewart Rodman, 225 South 15th Street, Philadelphia.

AMERICAN BOARD OF UROLOGY: Chicago, Feb. 10-14, 1951. Final date for filing applications is Sept. 1, 1950. Sec., Dr. Harry Culver, 7935 Sunnyside Road, Minneapolis 21.

BOARDS OF MEDICAL EXAMINERS

ALABAMA: *Examination.* Montgomery, June 27-29. Sec., Dr. D. G. Gill, 519 Dexter Avenue, Montgomery.

ALASKA: * Juneau, Sept. 5. Special examinations given on application. Sec., Dr. W. M. Whitehead, Box 140, Juneau.

ARKANSAS: * *Examination.* Little Rock, June 8-9. Sec., Dr. Joe Verser, Harrisburg. Homeopathic. Little Rock, June and November. Sec., Dr. Carl S. Bungart, 105 N. 14th St., Fort Smith. *Eclectic.* Little Rock, June 8-9. Sec., Dr. Clarence H. Young, 1415 Main Street, Little Rock.

CALIFORNIA: *Examination, Written.* San Francisco, June 19-22; Los Angeles, Aug. 21-24; Sacramento, Oct. 16-19. *Examination, Oral and Clinical for Foreign Medical School Graduates.* San Francisco, June 18; Los Angeles, Aug. 20; San Francisco, Nov. 12. *Reciprocity, Oral Examination.* San Francisco, June 17; Los Angeles, Aug. 19; San Francisco, Nov. 11. Sec., Dr. Frederick N. Scatena, 1020 N Street, Sacramento 14.

CONNECTICUT: * *Examination.* Hartford, July 11-12. Sec. to the Board, Dr. Creighton Barker, 160 St. Ronan St., New Haven. *Homeopathic.* Derby, July 11-12. Sec., Dr. Donald A. Davis, 38 Elizabeth St., Derby.

DELAWARE: *Examination.* Dover, July 11-13. *Reciprocity.* Dover, July 20. Sec., Dr. J. S. McDaniel, 229 S. State St., Dover.

FLORIDA: * Jacksonville, June 25-27. Sec. Dr. Frank D. Gray, 12 N. Rosalind Avenue, Orlando.

GEORGIA: *Examination.* Atlanta and Augusta, June. *Endorsement.* Atlanta, June. Sec., Mr. R. C. Coleman, 111 State Capitol, Atlanta 3.

HAWAII: *Examination.* Honolulu, July 10-13. Sec., Dr. I. L. Tilden, 1020 Kapiolani St., Honolulu.

IDAHO: Boise, July 10. Sec., Mr. Armand L. Bird, 305 Sun Bldg., Boise.

INDIANA: *Examination.* Indianapolis, June. Sec., Dr. Paul R. Tindall, 1138 K. of P. Bldg., Indianapolis.

IOWA: * *Examination.* Iowa City, June 12-14. Sec., Dr. M. A. Royal, 506 Fleming Building, Des Moines 19.

KANSAS: Kansas City, June 7-8. Sec., Dr. J. F. Hassig, 905 N. 7th Street, Kansas City.

KENTUCKY: *Examination.* Louisville, June 14-16. Sec., Dr. Bruce Underwood, 620 S. 3rd Street, Louisville 2.

LOUISIANA: New Orleans, June 8-10. Sec., Dr. Roy B. Harrison, 1507 Hibernia Bank Bldg., New Orleans.

MAINE: *Examination and Reciprocity.* Augusta, July 11-12. Sec., Dr. Adam P. Leighton, 192 State St., Portland.

MARYLAND: *Examination.* Baltimore, June 20-23. Sec. Dr. Lewis P. Gundry, 1215 Cathedral Street, Baltimore 1. *Homeopathic.* Baltimore, June 20-21. Sec., Dr. John A. Evans, 612 W. 40th St., Baltimore.

MASSACHUSETTS: *Examination.* Boston, July 11-14. Sec., Dr. George L. Schadt, Room 37, State House, Boston 33.

MICHIGAN: * *Examination.* Ann Arbor and Detroit, June 12-14. Sec., Dr. J. Earl McIntyre, 100 W. Allegan St., Lansing 8.

MISSISSIPPI: Jackson, June 20-21. Asst. Sec., Dr. R. N. Whitfield, Jackson 113.

MISSOURI: Examination. St. Louis, May 31-June 2 and June 7-9. Exec. Sec., Mr. John A. Hailey, Box 4, State Capitol Building, Jefferson City.

NEBRASKA: * *Examination.* Omaha, June 5-7. Director, Bureau of Examining Boards, Mr. Oscar F. Humble, 1009 State Capitol Building, Lincoln 9.

NEW HAMPSHIRE: Concord, Sept. 13. Sec., Dr. John Samuel Wheeler, 107 State House, Concord.

NEW JERSEY: *Examination.* Trenton, June 20-23. Sec., Dr. E. S. Hallinger, 28 West State Street, Trenton.

NEW YORK: *Examination.* Albany, Buffalo, New York and Syracuse, June 27-30. Sec., Dr. Jacob L. Lochner, Jr., 23 S. Pearl St., Albany.

NORTH CAROLINA: *Written.* Raleigh, June 19-22. *Endorsement.* Raleigh, June 19. Sec., Dr. Ivan Procter, 226 Hillsboro Street, Raleigh.

NORTH DAKOTA: *Examination.* Grand Forks, July 5-7. *Reciprocity.* Grand Forks, July 8. Sec., Dr. C. J. Glaspel, Grafton.

OHIO: *Examination.* Columbus, June 14-17. Sec., Dr. H. M. Platter, 21 W. Broad St., Columbus 15.

OKLAHOMA: * *Examination.* Oklahoma City, June 7-8. Sec., Dr. Clinton Gallaher, 813 Braniff Building, Oklahoma City.

PENNSYLVANIA: *Examination.* Philadelphia and Pittsburgh, July 11-14. Act. Sec., Mrs. Marguerite G. Steiner, 351 Education Bldg., Harrisburg.

PUERTO RICO: *Examination.* Santurce, Sept. 5. Sec., Mr. Luis Cueto Coll, Box 3717, Santurce.

SOUTH CAROLINA: *Examination.* Columbia, June 26-29. *Reciprocity.* First Monday of each month. Sec., Dr. N. B. Heyward, 1329 Blanding Street, Columbia.

SOUTH DAKOTA: * Sioux Falls, July 18-19. Sec., Dr. C. E. Sherwood, 300 First National Bank Bldg., Sioux Falls.

TEXAS: * *Examination.* Austin, June 19-21. Sec., Dr. M. H. Crabb, 1714 Medical Arts Bldg., Fort Worth 2.

UTAH: *Examination.* Salt Lake City, June. Dir., Dr. Frank E. Lees, 324 State Capitol Building, Salt Lake City.

VERMONT: *Examination.* Burlington, June 13-15. Sec., Dr. F. J. Lawliss, Richford.

VIRGINIA: *Examination.* Richmond, June 23-24. *Endorsement.* Richmond, June 22. Sec., Dr. K. D. Graves, 631 First St., S.W., Roanoke.

WEST VIRGINIA: *Examination.* Charleston, July 10-12. Sec., Dr. N. H. Dyer, Capitol Bldg., Charleston.

WISCONSIN: * Milwaukee, July 11-13. Sec., Dr. C. A. Dawson, River Falls.

WYOMING: *Examination.* Cheyenne, June 5. Sec., Dr. Franklin D. Yoder, Capitol Bldg., Cheyenne.

* Basic Science Certificate required.

BOARDS OF EXAMINERS IN THE BASIC SCIENCES

ALASKA: *Examination.* Juneau, last week in August. Sec., Dr. C. Earl Albrecht, Box 1931, Juneau.

ARIZONA: *Examination.* Tucson, June 20. Sec., Mr. Francis A. Roy, Science Hall, University of Arizona, Tucson.

CONNECTICUT. *Examination.* New Haven, June 10. Exec. Asst., State Board of Healing Arts, M. G. Reynolds, 110 Whitney Ave., New Haven.

FLORIDA: *Examination.* Gainesville, June 3. Sec., Mr. M. W. Emmel, University of Florida, Gainesville.

OREGON: Portland, June 17. Sec., Dr. C. D. Byrne, University of Oregon, Eugene.

SOUTH DAKOTA: Vermillion, June 2-3. Sec., Dr. Gregg M. Evans, 310 E. 15th Street, Yankton.

WISCONSIN: Milwaukee, June 3. Madison, Sept. 30. Sec., Mr. W. H. Barber, Scott and Watson Sts., Ripon.

Bureau of Medical Economic Research

MEDICAL ECONOMIC REVIEWS AND ABSTRACTS

Prepared by the Staff of the Bureau of Medical Economic Research

The Road Ahead: America's Creeping Revolution. By John T. Flynn. Cloth. $2.50. Pp. 160. Unabridged special edition. $1. Pp. 207. Distributed by The Committee for Constitutional Government, Inc., 205 E. 42nd St., New York 17, by Special Arrangement with the Publishers, The Devin-Adair Company, 23 E. 26th St., New York 10, 1949.

In Russia socialism entered through sudden violent revolution. In Great Britain it crept in gradually and almost imperceptibly. In both there is government control of industry and loss of individual liberty. John T. Flynn believes that America is following the path of Great Britain. Here socialism is occurring step by step.

Socialism is slowly taking possession of America for the same reason it took hold in Britain: because it is not recognized as socialism, because it is being marketed under various appealing labels which totally conceal its idenitty. In Britain, a handful of socialists, whose number never became greater than 4,000 and who called themselves the Fabian Society, cleverly laid their plans for establishing a socialist government. Realizing that they could gain power only if their true nature were disguised and if they proceeded gradually and through constitutional processes, they presented their program as "welfarism" and set themselves up as friends of the workers and the underprivileged. Their social reforms, which were presumably for the aid of the underprivileged, were actually a means of making the citizens dependent on the state for the correction of all ills. Every economic dislocation offered them an opportunity to gain favor through their empty promises of the good life, jobs and security for all. Finally, with the economic despair which followed the second World War, their promises gained them full control of the British government.

Mr. Flynn contrasts the Fabian promises with the tragic reality that is now England. Instead of a land of security for all, it is one of austerity for all. Poverty has not been eliminated; it has been distributed. And the freedom of the individual has been circumscribed by ever increasing government controls.

The author does not want America to be lured by the same empty promises. His book is a warning against the socialism that is slowly overtaking this country. This socialism is not the undisguised socialism of Norman Thomas, whose party has received an ever dwindling number of votes at the polls. Rather, it is the much more threatening socialism of the American "Fabians" which is being offered as the "Planned Economy." It is much more threatening because too many Americans do not recognize it and register their disapproval in elections. Following the course of their British counterpart, the American "Fabians" or "Economic Planners" have captured the labor unions and invaded the Democratic Party and have even penetrated our churches. They already occupy positions of power and leadership in national affairs.

Mr. Flynn notes that in this country, also, the socialists have gained ground in times of economic stress. The American capitalistic system at times is in serious need of repair. Mr. Flynn believes that there should be planning to prevent and eliminate disturbances in our economy. However, a plan to revive the economy of this country should not harbor a plot to replace it with a state-controlled socialist system.

This book is more than a warning. It is an exposé of those persons and groups who are trying to alter the fundamental structure of our society. It enables its readers to sweep aside the web of deception spun by the socialist forces in this country.

Bureau of Legal Medicine and Legislation

MEDICOLEGAL ABSTRACTS

Drunkenness: Admissibility in Evidence of Results of Chemical Tests for Intoxication.—The defendant was indicted and convicted of reckless operation of a motor vehicle while under the influence of intoxicating liquor and from such conviction appealed to the Supreme Court of New Hampshire.

In order to establish intoxication, the state relied in part on evidence of a chemical analysis of blood taken from the defendant about two hours after the collision. This evidence was received subject to the defendant's exception after a preliminary hearing by the court without a jury on the question of admissibility. Before receiving the evidence, the trial court made the following findings: "At the time the blood sample was taken from the defendant . . . he was under the influence of intoxicating liquor, that he was in a confused state of mind . . . due either to the alcoholic liquor which he had previously consumed and/or the injuries which he received in the accident, that said blood sample was obtained without force and that Sturtevant [defendant] gave his consent thereto, but the court is in doubt as to whether or not said Sturtevant was mentally capable at the time of freely giving his consent and that he was unaware that he was to be charged with a crime, that Trooper Watson stated to the respondent Sturtevant prior to the taking of his blood sample that the blood test might prove of value, or words to that effect." The Court supplemented these findings by adding "that Officer Watson told him, the defendant, that he, the officer, thought he should have it done for his own benefit."

At the close of the preliminary hearing at which the circumstances surrounding the taking of the blood specimen from the defendant were disclosed, the defendant voiced his objection to the receipt of evidence of the analysis thus: "We claim . . . that it is calling the defendant to furnish evidence against himself at a time when he was neither told nor in condition to know what his legal rights and what the implications of such procedure would be. . . ." There was no substantial change in the defendant's position, and the argument advanced before the Supreme Court is that the taking of the blood and the use made at the trial of the analysis which followed were a violation of the defendant's rights under Article 15 of the Bill of Rights, which provides in part: "No subject shall . . . be compelled to accuse or furnish evidence against himself."

At the outset, said the Supreme Court, it may be noted that the issue before us is not affected by the rules which govern the receipt in evidence of confessions of crime. The requirements which there pertain, designed to permit receipt of only such confessions as may be trustworthy, are not applicable here. A confession is "an acknowledgment in express words." "That which is not an assertion . . . can therefore not be within the scope of such a principle; its probative use is not testimonial, but circumstantial. . . . "It is apparent, the Supreme Court continued, that no assertion by the respondent is involved here, and no promise, threat or hope could affect the analysis.

If the defendant was "in a confused state of mind" and may not have been "mentally capable . . . of freely giving his consent" that circumstance can be material only because his consent was essential to an effective waiver of his constitutional privilege not to "furnish evidence against himself." If consent is material, said the Supreme Court, we are bound by the findings of the trial court to consider that it was not shown to have been intelligently given. We are thus squarely faced with the question of whether evidence of a blood analysis is admissible in evidence over the constitutional objection previously stated, where it appears that the sample analyzed was obtained without force, before arrest, at a time when the accused is not shown to have been capable of consent.

The constitutional provision invoked appears with varying phraseology in our Federal Constitution and those of most of the states; but because of their common historical origin, the variations are not considered to alter the essential meaning. Whatever their form, the purpose of the provisions may be regarded as uniform, to protect an accused "from any disclosure sought by legal process against him as a witness." Authorities establish the privilege to be one against testimonial compulsion only and that it is inapplicable to cases such as this, where the evidence is real rather than testimonial. As applied specifically to the question of making a blood test for intoxication, it must be recognized that the authorities are lacking in agreement on the effect of the privilege against self incrimination. We consider the better view, said the Supreme Court, and that which we do not adopt, to be that expressed by the Court in the recent case of State v. Cram, decided by the Supreme Court of Oregon. After reviewing the authorities at length, the Court in that case held that evidence such as was here reeceived was admissible over the constitutional objection here urged, although it there appeared that the respondent was unconscious and hence incapable of giving his consent at the time the blood specimen was taken. The Court then quoted with approval the language of Mr. Justice Holmes from a decision of the Supreme Court of the United States, which said: "But the prohibition of compelling a man in a criminal court to be a witness against himself is a prohibition of the use of physical or moral compulsion to extort communications from him, not an exclusion of his body as evidence when it may be material." Other authorities, said the Supreme Court of New Hampshire, have reached a comparable result where the evidence disclosed no compulsion or resistance in the taking of a specimen for analysis. The exception to the receipt of the evidence of the blood analysis was therefore overruled and the defendant's conviction was sustained. —*State v. Sturtevant, 70 A. (2d) 909 (New Hampshire 1950).*

Drunkenness: Admissibility in Evidence of Results of Chemical Tests.—The defendant was convicted in the county court for driving an automobile while intoxicated. From this conviction he appealed to the court of criminal appeals of Texas.

The defendant, arrested for driving while intoxicated, was taken to the police station, where he voluntarily gave a specimen of urine for examination and analysis for alcoholic content. The specimen was examined by a laboratory technician of the city-county health unit. This technician at the trial testified that the specimen showed an alcoholic content of 0.27 per cent and, over the objection of the defendant that he was not shown to be qualified, expressed his opinion that "the result obtained from a concentration of 0.27 per cent of alcohol in urine indicates a definite degree of intoxication in the person from whom the sample was taken."

When expert testimony is offered, said the court, the qualification of the witness to so testify should be fully shown, not only to aid the court in determining the admissibility of the testimony but also to aid the jury in determining the weight to be given thereto. It is sufficient, for instant purposes, to say that the trial court was authorized, in the exercise of his discretion, to permit the witness to testify as to the result of the urinalysis. There is no testimony, however, showing that the witness was qualified to express the opinion to the effect that the percentage of alcohol found in the defendant's urine indicated a definite degree of intoxication. To be authorized to express such opinion the witness was, of necessity, required to have technical training as to the human body, the effect of alcohol thereon and the degrees of intoxication produced by the use of alcohol. The witness did not profess to have knowledge, experience or training touching such matters. It is apparent, therefore, concluded the court of appeals, that the witness was not authorized to express an opinion as to defendant's intoxication.

The judgment of conviction was therefore reversed and the case remanded for a new trial.—*Lopez v. State, 225 S. W. (2d) 852, (Texas, 1950).*

Current Medical Literature

AMERICAN

The Association library lends periodicals to members of the Association and to individual subscribers in Continental United States and Canada for a period of five days. Three journals may be borrowed at a time. Periodicals are available from 1939 to date. Requests for issues of earlier date cannot be filled. Requests should be accompanied with stamps to cover postage (6 cents if one and 18 cents if three periodicals are requested). Periodicals published by the American Medical Association are not available for lending but can be supplied on purchase order. Reprints as a rule are the property of authors and can be obtained for permanent possession only from them.

Titles marked with an asterisk (*) are abstracted below.

American Journal of Clinical Pathology, Baltimore

20:1-98 (Jan.) 1950

Clinical Pathologist in Atomic Age. S. Warren.—p. 1.
Blood and Bone Marrow Studies in Renal Disease. I. R. Callen and L. R. Limarzi.—p. 3.
Study of Germinal Epithelium in Male Paraplegics. G. N. Stemmermann, L. Weiss, O. Auerbach and M. Friedman.—p. 24.
Mycologic Study of Seventy-One Autopsies. L. D. Haley and A. McCabe.—p. 35.
Precipitation of Abnormal Serums by Lugol's Solution. M. Salazar Mallen, E. Lozano Ugalde, M. Refugio Balcazar and others.—p. 39.
Hematologic and Chemical Changes in Donors During Bloodletting. J. Litwins, L. N. Sussman and M. D. Feltenstein.—p. 46.
Strain of Serratia Isolated from Urine. J. Gurevitch and D. Weber.—p. 48.

American Journal of Medical Sciences, Philadelphia

219:1-116 (Jan.) 1950

Effect of Halides on Antithyroid Action of Thiouracil and Propylthiouracil. R. H. Williams, H. Jaffe and B. Soloman.—p. 1.
Effect of Halides, Thiocyanate and Propylthiouracil upon Distribution of Radioiodine in Thyroid Gland, Blood and Urine. R. H. Williams, H. Jaffe and J. A. Taylor.—p. 7.
Clinical Effect of Nitrogen Mustard on Neoplastic Diseases. R. D. Bauer and L. A. Erf.—p. 16.
*Effect of War-Imposed Protein Free Diet on Blood Pressure Level in Essential Hypertension. J. Kohári-Kucharik.—p. 27.
*Surveys of Nutrition of Populations: Iron and Anemia. J. B. Youmans, E. W. Patten, R. Kern and others.—p. 30.
Deaths from Acute Rheumatic Fever in Texas: Relationship to Mean January Temperature. H. E. Heyer, A. E. Hansen, D. W. Chapman and others.—p. 40.
Cephalin-Cholesterol Flocculation Reaction in Rheumatic Heart Disease—Part I. R. W. Kissane, R. S. Fidler, T. E. Clark and J. J. Conn.—p. 48.
Study of Crystalline Albumin, Gamma Globulin and Total Protein in Cerebrospinal Fluid of 100 Cases of Multiple Sclerosis and Other Diseases. E. A. Kabat, D. A. Freedman, J. P. Murray and V. Knaub.—p. 55.
Urine Volume, Non-Protein Nitrogen and Pigment Cast Studies in Rabbits with Hemoglobinuric Nephrosis. J. J. Lalich.—p. 65.
Myasthenia Gravis in Case of Malignant Thymoma Resistant to Neostigmine Therapy. J. A. Rider and R. McDonald.—p. 71.
Vital Capacity in Adults with Heart Disease: Its Relation to Age, Degree of Cardiac Enlargement and Type of Valvular Lesion. J. D. Gardam.—p. 76.
Electrocardiographic Changes Induced by Cold Application to Various Body Sites in Patients with Angina Pectoris—Preliminary Report. B. Berman and J. McGuire.—p. 82.
Conversion of Auricular Fibrillation to Sinus Rhythm After Digitoxin Administration. J. S. Feibush.—p. 86.
Fatal Hepatitis. J. R. Snavely.—p. 89.
Psychiatric Contributions to Treatment of Obesity. S. Bayles.—p. 104.

Effect of Protein-Free Diet on Essential Hypertension.—Kohári-Kucharik points out that during the siege of Budapest in 1945 the supply of animal proteins became exhausted. This circumstance made it possible to study the influence of a diet free of animal proteins on hypertension. He reports observations on patients with hypertension who had been treated two to five years and the majority of whom attended the outpatient clinic fortnightly. Because of the war, only 39 of the original 150 patients could be followed. The period during which animal proteins were unobtainable lasted about ten months. The 39 patients with long-standing essential hypertension did not show any consistent change in blood pressure after this long period of protein deprivation.

Nutrition Surveys: Iron and Anemia.—Youmans and associates report on the nutrition of a rural population of some 1,200 persons in middle Tennessee, with respect to the intake of iron, signs and symptoms of anemia and the condition of the blood. The characteristics of the population, the general methods of the study and the results with respect to calories, protein vitamin A, vitamin D, calcium and vitamin C had been given in previous papers. The daily intake of iron was found in a large percentage of the population to be below the levels commonly recommended. Anemia, as measured by the concentration of hemoglobin, was found in approximately 14 per cent of the population, but there was a wide variation in frequency in the various age, sex and racial groups. The incidence was greatest in female subjects at puberty and older and generally greater in Negro than in white subjects. In general, a reduction in red cells below normal was more frequent (20 per cent) than a reduction in hemoglobin. A decreased mean cell volume (microcytosis) was found in a considerable number of those 16 years of age and older, and there was a decrease in the mean corpuscular hemoglobin in the female subjects in this age group. An increased cell volume (macrocytosis) in over one third of the population was a surprising finding. In 166 persons the mean corpuscular volume was more than 4 standard deviations above upper normal limits (Wintrobe). Of this latter group, 89 and 97 per cent (white and Negro, respectively) had red cell counts below normal and 35 to 51 per cent had below 4 million. Five of these subjects were given a single injection of 20 mg. of folic acid and responded with slight reticulocytosis. Some had a higher than normal mean corpuscular hemoglobin. The cause of the high incidence of macrocytic anemia has not been definitely explained; some have ascribed such anemias to deficiencies in the vitamin B complex but also to deficiencies in other nutrients.

American Journal of Surgery, New York

79:1-218 (Jan.) 1950. **Partial Index**

Anal Ducts and Their Clinical Significance. G. L. Kratzer.—p. 32.
Hemorrhoids: Etiology and Pathology. O. C. Gass and J. Adams.—p. 40.
Present Status of Injection Treatment of Internal Hemorrhoids. R. V. Terrell and C. C. Chewning Jr.—p. 44.
Study of Injection Treatment of Internal Hemorrhoids Using 5 Per Cent Phenol-In-Oil. A. C. Pfeifer.—p. 49.
Hidradenitis Suppurativa Involving Para-Anal Region. J. B. Christensen.—p. 61.
Combined Abdominoperineal Resection. C. W. Mayo.—p. 72.
Perineo-Abdominal Excision of Rectum in One Stage. W. B. Gabriel.—p. 76.
Anorectal Malignant Melanoma. R. W. Raven.—p. 85.
Epidermoid Carcinoma of Anus and Rectum: Review of 125 Cases. G. E. Binkley.—p. 90.
Surgical Principles in Treatment of Pilonidal Cyst and Its Complications. J. C. Harberson and E. S. Brintnall.—p. 101.
Coccygodynia: Mechanism of Its Production and Its Relationship to Anorectal Disease. G. H. Thiele.—p. 110.
Low Back and Rectal Pain from Orthopedic and Proctologic Viewpoint with Review of 180 Cases. S. Schapiro.—p. 117.
Sacral Block Anesthesia in Proctologic Operations. J. S. Lundy.—p. 137.
Pentothal Sodium in Anorectal Surgery: Analysis of 1,500 Cases. R. E. Crigler.—p. 140.
Spinal Anesthesia in Proctology. A. G. Carmel.—p. 144.
Surgical Importance of Composite Longitudinal Muscle of Anal Canal, External Sphincter and Levator Ani Muscles. C. N. Morgan.—p. 151.
Anatomy of Pelvic Diaphragm and Anorectal Musculature as Related to Sphincter Preservation in Anorectal Surgery. H. Courtney.—p. 155.
Plastic Repair of Incontinent Sphincter Ani. P. C. Blaisdell.—p. 174.

Bulletin of Johns Hopkins Hospital, Baltimore

85:409-452 (Dec.) 1949

Low Electrical Skin Resistance in Region of Pain in Painful Acute Sinusitis. T. E. Van Metre Jr.—p. 409.
Agglutination of Red Cells Altered by Action of Newcastle Disease Virus: I. Effect of Chicken Sera from Infected Birds on Sensitized Cells. F. B. Bang and R. Libert.—p. 416.
Spinal Subdural Abscess Due to Congenital Dermal Sinus and Accompanying Changes in Autonomic Nervous System. A. B. King and C. P. Richter.—p. 431.

Delaware State Medical Journal, Wilmington

22:1-22 (Jan.) 1950. **Partial Index**

Human Dentition. W. F. Melson.—p. 1.
Caries Control. J. D. Brown and H. H. McAllister.—p. 4.
Bacillary Dysentery and Gastro-Enteritis: Diagnosis and Treatment of 18 Cases. E. G. Scott.—p. 9.
Dermoid of Conus Medullaris (Urogenital Complications). B. S. Vallett.—p. 14.
Blue Cross Protects the People—Who Protects Blue Cross? P. R. Hawley.—p. 16.

22:23-54 (Jan.) 1950. **Supplement**

New Light on History of Medicine in Delaware. W. E. Bird.—p. 23.

Journal of Clinical Investigation, Cincinnati

28:1387-1614 (Nov. [Part 2]) 1949. **Partial Index**

Hemodynamic Effects of Hypotensive Drugs in Man: II. Dihydroergocornine. E. D. Freis, J. R. Stanton, J. Litter and others.—p. 1387.
Effect of Cation Exchange Resin on Electrolyte Balance and Its Use in Edematous States. L. Erwin, E. Y. Berger, B. Rosenberg and R. Jackenthal.—p. 1403.
*Carbon Tetrachloride Poisoning in Man: I. Mechanisms of Renal Failure and Recovery. J. H. Sirota.—p. 1412.
Normal Respiratory and Circulatory Pathways of Adaptation in Exercise. R. A. Bruce, F. W. Lovejoy Jr., R. Pearson and others.—p. 1423.
Studies in Methionine Metabolism: II. Fasting Plasma Methionine Levels in Normal and Hepatopathic Individuals in Response to Daily Methionine Ingestion. L. W. Kinsell, H. A. Harper, G. K. Giese and others.—p. 1439.
Protamine (Salmine) Sulphate, Heparin, and Blood Coagulation. A. F. Portmann and W. D. Holden.—p. 1451.
Effect of Theophylline Ethylene Diamine on Renal Function in Control Subjects and in Patients with Congestive Heart Failure. J. O. Davis and N. W. Shock.—p. 1459.
Electrophoretic Studies of Serum Proteins in Biliary Cirrhosis. K. Sterling and W. E. Ricketts.—p. 1469.
*Electrophoretic Studies of Serum Proteins in Virus Hepatitis. W. E. Ricketts and K. Sterling.—p. 1477.
Influence of Adrenal Cortex on Body Water Distribution and Renal Function. M. Gaudino and M. F. Levitt.—p. 1487.
Electrolyte Balances in Male Infant with Adrenocortical Insufficiency and Virilism. Effect of Desoxycorticosterone Acetate and Salt Therapy with Special Reference to Potassium. H. L. Barnett and H. McNamara.—p. 1498.
Thrombin Formation: II. Effects of Lysin (Fibrinolysin, Plasmin) on Prothrombin, Ac-Globulin and Tissue Thromboplastin. J. H. Lewis, A. C. Howe and J. H. Ferguson.—p. 1507.
Prothrombin Consumption, Serum Prothrombic Activity and Prothrombin Conversion Accelerator in Hemophilia and Thrombocytopenia. B. Alexander and G. Landwehr.—p. 1511.
Multiple-Balloon-Kymograph Recording of Intestinal Motility in Man with Observations on Correlation of Tracing Patterns with Barium Movements. W. P. Chapman and W. L. Palazzo.—p. 1517.
Renal Tubular Secretion of Potassium in Man. A. Leaf and A. A. Camara.—p. 1526.
Circulatory Dynamics Before and After Exercise in Subjects With and Without Structural Heart Disease During Anxiety and Relaxation. I. P. Stevenson, C. H. Duncan and H. G. Wolff.—p. 1534.
Role of Oxygen in Regulation of Erythropoiesis. Depression of Rate of Delivery of New Red Cells to Blood by High Concentrations of Inspired Oxygen. J. C. Tinsley Jr., C. V. Moore, R. Dubach and others.—p. 1544.
Relationship Between Serum Lipids and Skin Xanthomata in 18 Patients with Primary Biliary Cirrhosis. E. H. Ahrens Jr. and H. G. Kunkel. —p. 1565.

Carbon Tetrachloride Poisoning in Man.—Sirota studied the renal function of 4 male patients with acute renal damage due to inhalation of carbon tetrachloride. In describing the tests and the results obtained, the following abbreviations were used: IN for inulin, CR for endogenous creatinine, PAH for p-aminohippurate and C for clearance; thus C_{in} in clearance of inulin, Tm_{pah} and Tm_d are tubular maximal excretory capacity for p-aminohippurate and diodrast® (iodopyracet injection), respectively. E is renal extraction ratio, RBF is renal blood flow and U/P ratio is ratio of urine concentration to plasma concentration. Renal venous blood was obtained by catheterization of the right renal vein. P-aminohippurate was used as the test substance. The recovery of renal function following acute renal failure due to carbon tetrachloride poisoning is characterized by three clinical phases. The first phase starts with the cessation of oliguria and is associated with rising plasma creatinine and urea concentrations in spite of an adequate urine flow. It lasts one to three days, during which time there is little change in C_{in}, C_{cr} and C_{pah}. The second phase starts with a rapid decline in the plasma urea and creatinine levels and a simultaneous rapid rise in C_{in}, C_{cr} and C_{pah}, which reach 40 to 70 per cent of normal by the fortieth day from the onset of oliguria. The third phase, starting about the fortieth day, is characterized by gradual improvement in renal blood flow and glomerular filtration, so that the lower limit of normal is reached between the hundredth and two hundredth day. During this phase the ability to elaborate a maximally concentrated urine is recovered. During the early part of recovery phases Tm_{pah} reached high normal or supernormal values in 3 of the patients. These gradually declined to the expected norm. The ratios C_{in}: Tm_{pah} and C_{pah}; Tm_{pah}, however, were significantly lower than normal in all 4 patients when last determined on the sixtieth, two hundred fiftieth, three hundred seventh and three hundred thirty-first day, respectively, suggesting some residual vascular damage.

Serum Proteins in Virus Hepatitis.—Ricketts and Sterling describe investigations of the alterations of serum proteins in the course of a virus hepatitis, including its later stages. Electrophoretic runs were performed with standard apparatus and technic. Ten volunteer subjects with normal tests of hepatic function served as controls. Twenty-one clinically typical cases of hepatitis were studied. Electrophoretic analyses of serum proteins in 10 cases of acute virus hepatitis revealed diminished albumin values in all, elevated gamma-globulins in 7 of the 10 and elevated beta-globulins in the same number. Cases of severe acute hepatitis showed in general more pronounced changes than milder cases, but no strict correlation existed. Serial electrophoretic analyses disclosed reversion of the serum proteins to normal in 2 cases of acute hepatitis, but persistent abnormalities were observed in 3 cases despite clinical recovery. Late follow-up studies on serums from 11 patients who had clinically recovered from acute virus hepatitis 10 to 36 months previously revealed residual abnormalities in the electrophoretic patterns of 8 of the 11 serums.

Journal of Experimental Medicine, New York

91:1-114 (Jan.) 1950

Localization of Antigen in Tissue Cells: II. Improvements in Method for Detection of Antigen by Means of Fluorescent Antibody. A. H. Coons and M. H. Kaplan.—p. 1.
Id.: III. Cellular Distribution of Pneumococcal Polysaccarides Types II and III in Mouse. M. H. Kaplan, A. H. Coons and H. W. Deane. —p. 15.
Id.: IV. Antigens of Rickettsiae and Mumps Virus. A. H. Coons, J. C. Snyder, F. S. Cheever and E. S. Murray.—p. 31.
Multiplication of Certain Neurotropic Viruses in Rabbit Eye Following Intraocular Inoculation. J. R. Overman and W. F. Friedwald.—p. 39.
Further Studies on Associative Reactions of Pneumonia Virus of Mice (PVM) and Influenza Viruses: Combination with Various Animal Tissues and Adsorbents. F. M. Davenport and F. L. Horsfall Jr. —p. 53.
Lack of Identity in Neutralizing and Hemagglutination-Inhibiting Antibodies Against Influenza Viruses. D. L. Walker and F. L. Horsfall Jr.—p. 65.
Neoplastic Potentialities of Mouse Embryo Tissues: V. Tumors Elicited with Methylcholanthrene from Pulmonary Epithelium. W. E. Smith. —p. 87.
Immunochemical Studies on Blood Groups: X. Preparation of Blood Group A and B Substances and Inactive Substance from Individual Horse Stomachs and of Blood Group B Substance from Human Saliva. H. Baer, E. A. Kabat and V. Knaub.—p. 105.

Journal of International College of Surgeons, Chicago

13:1-138 (Jan.) 1950

Tumors of Bladder. T. J. Kirwin.—p. 1.
Primary Gastroduodenal Resection for Acute Perforating Peptic Ulcer. F. S. Guerrero.—p. 20.
Selection of Surgical Procedure in Treatment of Cancer of Rectum. H. E. Bacon and I. Sauer.—p. 24.
Connective Tissue and Its Derivatives: Surgical Significance in Light of Embryogeny. T. Kalima.—p. 30.
Value of Cystoscopic Photography. L. E. McCrea.—p. 35.
Treatment of Large and Recurrent Postoperative Inguinal Hernia. L. F. Watson.—p. 37.
Full Thickness Skin Graft in Repair of Voluminous Hernias. M. Behrend and A. Behrend.—p. 41.
Present Status of Surgical Problem of Hyperplasia of Prostate. C. P. Mathé.—p. 46.
Curare and Shock. L. Imperati, G. D'Errico and A. Ruggiero.—p. 54.
Headache. R. Jaeger.—p. 57.
Obstetrical Emergencies. W. B. McGee.—p. 64.
Clinicopathologic Study of One Hundred Consecutive Thyroid Procedures. B. J. Ficarra.—p. 71.
Determination of Anesthetic Procedure of Choice. R. Weyl.—p. 78.
Tuberculosis of Urinary Tract: Medical-Surgical Management. M. Schattyn.—p. 85.
Plea for Complete Adenoidectomy. T. F. Furlong Jr.—p. 88.
Acute Intussusception in Adults: Cause and Treatment: Report of 2 Cases. J. H. Brady.—p. 91.
Surgical Therapy of Carcinoma of Larynx. R. Aurel.—p. 93.

Journal-Lancet, Minneapolis

70:1-32 (Jan.) 1950

Rehabilitation of Amputee. G. Gullickson and F. J. Kottke.—p. 1.
Hormone Therapy of Advanced Cancer of Breast. S. W. Arhelger.—p. 6.
Hypoparathyroidism: Case Report. A. E. Moe.—p. 10.
Care of Pregnant Diabetic. W. B. Stromme.—p. 13.
Incidence of Types of Cardiac Deaths in 50,730 Autopsies. B. J. Clawson.—p. 15.
Treatment of Pemphigus Vulgaris. I. Fisher.—p. 18.
Lipoid Nephrosis (Case of Nephrosis in White Boy 26 Months of Age). R. B. Tudor.—p. 21.
Diabetes Detection in North Dakota. E. A. Haunz.—p. 24.
Clinical Evaluation of Chlor-Trimeton. W. S. Eisenstadt.—p. 26.

Journal of National Malaria Society, Columbia, S. C.

8:247-350 (Dec.) 1949. **Partial Index**

Effectiveness Against Flies and Mosquitoes of DDT Applications to Clay, Palm, and Straw Surfaces. S. Sundararaman and R. L. Peffly.—p. 267.
Preliminary Field Studies on Use of Heavy Dosages of DDT and Benzene Hexachloride as Residual Mosquito Larvicides. W. Mathis and K. D. Quarterman.—p. 270.
Effects of X-Irradiation on Plasmodium Gallinaceum and Plasmodium Lophurae Infections in Young Chicks. B. E. Bennison and G. R. Coatney.—p. 280.
Observations on Plasmodium Lophurae Infections in White Pekin Ducklings Transfused with Duck and Chick Erythrocytes. E. R. Becker, A. A. Marousek and C. E. Brodine.—p. 290.
Effect of Human Blood on Plasmodium Knowlesi Infection in Monkeys. R. H. Rigdon and D. Breslin.—p. 298.

Journal of Nervous and Mental Disease, New York

111:1-90 (Jan.) 1950

Amyotrophic Lateral Sclerosis. A. P. Friedman and D. Freedman.—p. 1.
Toward Integrative Conception of Mental Disorder. J. Marmor and E. Pumpian-Mindlin.—p. 19.
Multiple Sclerosis (Encephalomyelitis Disseminata Periaxialis) and Vegetative Nervous System: I. Gastric Disorders in Multiple Sclerosis. L. Hess.—p. 30.
Course and Outcome of Visual Agnosia. A. Adler.—p. 41.
Preconvulsive Paroxysmal Electroencephalographic Changes After Metrazol Injection. E. Ziskind and N. A. Bercel.—p. 52.

Journal of Pediatrics, St. Louis

36:1-142 (Jan.) 1950

*Pseudohypoparathyroidism (Seabright Bantam Syndrome). C. U. Lowe, A. J. Ellinger, W. S. Wright and H. M. Stauffer.—p. 1.
Glycogen Disease Resembling Mongolism, Cretinism, and Amytonia Congenita: Case Report and Review of Literature. D. H. Clement and G. C. Godman.—p. 11.
*Use of Positive Pressure as Aid in Handling Respiratory Paralysis from Anterior Poliomyelitis. R. L. Masland, R. B. Lawson and W. M. Kelsey.—p. 31.
Purpuric Manifestations Occurring in Measles in Childhood. S. D. Mills.—p. 35.
Urinary Lysozyme: I. Identification and Measurement. A. T. Wilson.—p. 39.
Id.: II. Lysozymuria in Healthy Children and in Children with Miscellaneous Diseases (Sex Difference). A. T. Wilson and W. P. Hadley.—p. 45.
Development of Aerobic Bacterial Flora of Throat in Newborn Babies. J. W. Smith and A. L. Bloomfield.—p. 51.
*Infectious Lymphocytosis: Report of Epidemic in Children. B. K. Lemon and D. H. Kaump.—p. 61.
Treatment of Acute Leucemias of Childhood with Folic Acid Antagonists. E. J. Weber, F. E. Karpinski Jr. and R. W. Heinle.—p. 69.
Hyaluronidase: Further Evaluation in Pediatrics. J. Schwartzman and M. Levbarg.—p. 79.
Methyl Testosterone and Plasma for Premature Infants. A. M. Earle.—p. 87.

Pseudohypoparathyroidism.—Lowe and co-workers report 1 case of pseudohypoparathyroidism in a girl who at the time of her first admission to the hospital was 2 months of age. She was readmitted to the hospital several times at various intervals and was aged 4 years and 8 months when she was discharged for the last time. Pseudohypoparathyroidism is a rare disease, for which the term Seabright bantam syndrome was suggested. The Seabright bantam roosters have female tail feathers; presumably the feathers do not respond to male sex hormones in this species of bird as they do in other species. Failure of response to parathormone was suggested to be responsible for the chemical aberrations in the blood present in this syndrome. The sequence of events in the pathogenesis of the patient in the authors' case was as follows: her primary disease was steatorrhea. This had been present since very early in life, though the cause could not be determined. Steatorrhea caused malabsorption of the fat-soluble vitamins. Secondary to the malabsorption of vitamin D, the patient failed to absorb calcium from her intestines. This in turn caused hypocalcemia and tetany. At 4 months of age the patient had values of calcium and phosphorus in her blood consistent with hypoparathyroidism. Concentration of calcium and phosphorus in the blood returned to normal levels after parenteral administration of large doses of vitamin D. Elevated serum alkaline phosphatase was present even during a period when there was neither clinical nor laboratory evidence of liver disease. There was lack of evidence of osteomalacia in roentgenograms of the bones, but there was a definite interference with normal trabecular structure, this being characterized by intermingling of abnormally dense with abnormally rarified areas. The patient presented unusually dense metaphysial bone. Phosphate diuresis failed to appear after intravenous administration of parathyroid extract. If one accepts the fact that the patient had aberrations in calcium and phosphorus metabolism secondary to steatorrhea, the initial bone disease must be considered as osteomalacia, and the elevated serum alkaline phosphatase, which is ordinarily not noted in hypoparathyroidism, seems to be compatible with this. It might explain why the bones showed rarifaction as well as increased densities on roentgenologic examination. The failure of renal response to parathyroid extract might be likened to an "escape" phenomenon in which, because of continued overstimulation, the kidneys had become refractory to parathormone. Patients and experimental animals frequently become refractory to prolonged administration of parathyroid extract. Animals maintained on low calcium diets rapidly become resistant to parathyroid extract. Some cases of the Seabright bantam syndrome or conditions simulating it may have as their cause chronic overstimulation of the renal tubules by the parathyroid gland, with occasional failure of response of these end organs.

Respiratory Paralysis in Poliomyelitis.—Masland and co-workers used positive pressure breathing in 10 patients with the respiratory or bulborespiratory forms of poliomyelitis during the 1948 epidemic in North Carolina. Severe pulmonary edema was reversed by the use of the positive pressure respirator in 3 patients, and pulmonary edema was probably prevented in some of the other patients. The progressive hypoventilation which develops in the paralyzed patient is due to pulmonary edema rather than to atelectasis in many instances. The intermittent use of positive pressure breathing leads to improvement in patients of this type. Positive pressure respiration has definite value in treatment of respiratory paralysis in poliomyelitis both in increasing the ease of movement of the patient and in the prevention and treatment of certain of the pulmonary complications which develop in the paralyzed patient.

Infectious Lymphocytosis.—Lemon and Kaump report an epidemic of mild infectious lymphocytosis in 36 small children of a total population of 106 children from the Sarah Fisher Home for Children in Detroit. The children ranged in age from 18 months to 6 years; except for 3 all were between the ages of 2 and 3 years. Forty-nine children were examined and could be placed in one of three groups determined by the total leukocyte count and by numerical alterations in either or both of the lymphocyte and eosinophil counts. In group 1 were included 17 patients who had total leukocyte counts of over 15,000 per cubic millimeter and lymphocyte counts greater than 70 per cent or eosinophil counts over 3 per cent. There were 5 of the 17 patients in whom it was felt that a more or less complete cycle of the disease was represented in the study; in 9 patients the lymphocytosis was in a subsiding phase at the time of the beginning of the authors' study, and 3 patients were believed to be in a chronic or slowly regressing phase of lymphocytosis. In group 2 were included 19 children who had total leukocyte counts less than 15,000 per cubic millimeter but with elevation of either or both of the lymphocyte or eosinophil count. In group 3 were included 13 children in whom the hematologic values were within normal range and who served as controls. Clinical observations were not suggestive of any specific clinical picture of the disease. It is apparently not associated specifically with respiratory infections or hepatitis but probably does occur in epidemic form. Its course consists of an acute or ascending phase, a subsiding or descending phase and a chronic or variable phase. The disease is characterized hematologically by an absolute leukocytosis and lymphocytosis of varying degrees which may persist four to seven weeks in the acute and seven to twelve weeks in the subsiding and late phases. The lymphocyte morphology is not pathognomonic, although large-sized mature cells tend to predominate in the phase of greatest leukocytosis and again in the phase immediately following recovery as indicated by a return to normal of the total leukocyte level. Eosinophilia is frequently observed in the recovery phase. There is a high percentage of lymphocytes of normal mature form in the bone marrow, thus distinguishing infectious lymphocytosis

from infectious mononucleosis and lymphatic leukemia. The disease is apparently benign and self limited. Sulfadiazine and/or penicillin had no beneficial effect on the course of the disease.

Journal of Thoracic Surgery, St. Louis

19:1-166 (Jan.) 1950

*Surgical Treatment of Mitral Stenosis: II. Progress in Developing Controlled Valvuloplastic Technique. D. E. Harken, L. B. Ellis and L. R. Norman.—p. 1.
*Surgery of Mitral Stenosis. C. P. Bailey, R. P. Glover and T. J. E. O'Neill.—p. 16.
Acidosis During Thoracic Surgery. H. K. Beecher and A. J. Murphy. —p. 50.
Blood Volume Changes in Tuberculous Patients Treated by Thoracoplasty. F. F. Allbritten Jr., H. Lipshutz, B. J. Miller and J. H. Gibbon Jr.—p. 71.
Pulmonary Circulation and Alveolar Ventilation—Perfusion Relationships After Pneumonectomy. A. Cournand, R. L. Riley, A. Himmelstein and R. Austrian.—p. 80.
Fibrosarcoma of Bronchus: Report of Case Diagnosed by Bronchoscopy and Treated by Pneumonectomy. J. Carswell Jr. and N. H. Kraeft. —p. 117.
Fibrosarcoma of Bronchus. H. Black.—p. 123.
Expectoration of Fibrosarcoma: Patient Well Four Years Later. J. J. Curry and J. E. Fuchs.—p. 135.
Foregut Cyst of Mediastinum. M. A. Cassel, R. T. Cunningham and W. Weisel.—p. 138.
Treatment of Simple Spontaneous Pneumothorax. P. C. Curti and T. Poulsen.—p. 145.
Anesthetic Blocking of Vagus, Sympathetic and Phrenic at Neck in Thoracic Surgery—Its Protective Action on Blood Pressure: Experimental Researches. F. Soave.—p. 157.

Surgical Treatment of Mitral Stenosis.—Harken and co-workers employed surgical treatment in 8 of 25 patients with mitral stenosis. Mitral valvuloplasty was performed in 5 patients, with 3 deaths. Artificial interatrial shunts were produced through the provision of septal defects in 2, while cardiac denervation was performed in 1. Death occurred in the first of the 3 fatal cases because the devastating effect of tachycardia was not appreciated. The second death resulted on the operating table from uncontrolled blood loss and the third from pulmonary edema on the fifth postoperative day. Autopsy revealed that too little valvuloplastic incision had been made. The significant point in stenosis is the pronounced thickening in a ring of dense fibrous tissue at and just behind the free margin. This ring is continuous across the fused commissural zones and prevents the closure of the valve in systole, just as it prevents opening of the valve in diastole. Considerable improvement in the valvular action of the thickened mitral funnel can be expected if this ring is broken, preferably by incision or wedge resection in both commissural zones. An operating tunnel is presented which provides an opportunity for more deliberate, better controlled intracardiac operation in human valvuloplasty. Completed postoperative evaluation in 1 of the patients showed improvement associated with the valvuloplastic operation. Two new principles of mitral valvuloplastic surgery were evolved: Blind intracardiac maneuvers must be well controlled and deliberate. There must be the least possible stimulation of the ventricular endocardium during intracardiac operation.

Surgery of Mitral Stenosis.—Bailey and co-workers report on surgical treatment in 15 patients with mitral stenosis. Commissurotomy was performed on 3 men and 4 women between the ages of 21 and 39, with excellent results in 4 and 3 deaths. Commissurotomy is a simple, direct, effective and safe procedure. It accomplishes relief of mitral stenosis by restoring valve function without the production of additional mitral regurgitation. Digital guidance in the performance of accurate valve surgery is essential until a method of direct vision becomes established. The left auricular appendage is the most satisfactory route of approach to the mitral valve. The auricular appendage must be ligated at the conclusion of the procedure to prevent arterial embolization. An enlarged left ventricle in a case of supposed "pure" mitral stenosis is indicative of some additional significant valve lesions, such as aortic stenosis or regurgitation or mitral regurgitation, and presents probably a contraindication to commissurotomy. In 2 of the remaining 8 patients the interventions were exploratory or only attempted, for both patients died before the heart was entered. An incision was inadvertently made across the anteromedial valve cusp rather than through the posterior commissure in 2 other patients, resulting in severe mitral regurgitation and death. An interauricular shunt was produced in 1 patient. Simple digital dilation of the mitral orifice was carried out in the 3 remaining patients because of their poor condition. Two of these died, while 1 was greatly improved. Patients with mitral stenosis must be carefully studied and selected for operation. In addition to clinical evaluation this should include cardiac catheterization for determination of pulmonary vascular pressures, ballistocardiography and other physiologic studies of cardiac output. Venous shunts for the treatment of mitral stenosis are of some value, although their occasional effects on cardiac output, the right ventricle and the lesser circulation must be kept in mind.

Michigan State Medical Society Journal, Lansing

49:1-128 (Jan.) 1950

Experiences with Routine Rh Typing in Obstetrics: Observations in Series of 100 Rh Negative Pregnant Women. C. W. Aldridge and R. M. Campbell.—p. 51.
Extra-Abdominal Causes Producing Acute Abdominal Signs. R. Barnes. —p. 59.
Acute Surgical Conditions of Abdomen. A. S. Jackson.—p. 64.
Recto-Urethral Fistula. J. F. Wenzel and E. A. Jenkins.—p. 67.
Mental Illness: Administrative, Preventive and Therapeutic Considerations. A. E. Eyres.—p. 69.
Place of Psychiatry in Industry. L. E. Himler.—p. 75.
Iatrogenicity in Medicine. F. G. Ebaugh.—p. 79.
Observations on a Recent Journey in Sweden. B. H. Larsson.—p. 85.
Rehabilitation of Hard-of-Hearing School Child: Detroit's Plan. L. Galdonyi.—p. 89.
Family Guidance. J. M. Dorsey.—p. 92.

Nebraska State Medical Journal, Lincoln

35:1-28 (Jan.) 1950

Jaundice in the Newborn. J. A. Bigler.—p. 4.
Hydatidiform Mole and Chorio-Epithelioma. E. M. Dorr.—p. 8.
Consideration for Surgery in Management of Bleeding Peptic Ulcer. R. R. Best.—p. 11.
Pre- and Postoperative Care of Gastric Surgical Patients. W. P. Kleitsch.—p. 16.
Uteroplacental Apoplexy (Couvelaire Uterus): Review with Report of 2 Cases. W. L. Rumbolz and R. A. McShane.—p. 19.

35:29-64 (Feb.) 1950

Serum Albumin in Treatment of Toxemias of Pregnancy. E. M. Dorr. —p. 32.
Differential Diagnosis of Jaundice. F. Bayless.—p. 35.
Influence of Cancellous Bone in Healing of Fractures Requiring Open Reduction. J. E. M. Thomson.—p. 38.
Bronchial Adenoma: Case Report. H. D. Hilton, F. H. Tanner and G. E. Place.—p. 41.
Bronchogenic Carcinoma. J. J. O'Neil.—p. 44.

New England Journal of Medicine, Boston

242:39-76 (Jan. 12) 1950

Practicing Physician in the Field of Preventive Medicine. W. G. Smillie.—p. 39.
Effect of Nasal and Sinus Surgery upon Manifestations of Allergy. F. L. Weille.—p. 43.
*Fatal Agranulocytosis Following Therapy with "Presidon" (3,3-Diethyl-2,4-Dioxotetrahydropyridine), New Sedative Hypnotic Agent. A. H. Covner and S. L. Halpern.—p. 49.
*Quinidine as Cause of Thrombocytopenic Purpura: Report of Case. J. W. Norcross.—p. 53.
Aseptic Intestinal Decompression During Surgery. J. O'L. Nolan and G. C. Finley.—p. 54.
Toxicology. J. T. Walker.—p. 56.
Carcinoma of Left Breast, with Generalized Metastases Including Right Breast, Pleura, Pulmonary Lymphatics, Liver, Spleen and Bone Marrow.—p. 61.
Pulmonary Endarteritis (Ayerza's Syndrome). Cor Pulmonale.—p. 64.

Fatal Agranulocytosis Following Use of New Sedative.—Covner and Halpern point out the danger involved in the use of one of the recently introduced nonbarbiturate sedative drugs, presidon (3,3-diethyl-2,4-dioxotetrahydropyridine) (pyrithyldione). The drug was advertised as predictable in its effect, rapid in onset, with negligible side effects, and completely nontoxic and safe. The authors present the history of a woman, aged 64, who died after having been given a total dose of 1.8 Gm. of the drug in five days. Although the patient had also been given dihydromorphinone (dilaudid®) hydrochloride and barbiturates, the authors present evidence to show why these should not be incriminated as the toxic agents in this case. The patient was given antibiotics in the form of penicillin and streptomycin, blood transfusions and leukopoietic agents, including pentose nucleotide, pyridoxine and liver extract. The fatal out-

come was consistent with the fact that the period of total lack of circulating granulocytes was relatively long, that the patient was an elderly person with poor previous health and poor tissue resistance and that the bacterial invasion was with Pseudomonas aeruginosa (Bacillus pyocyaneus), an organism known to be resistant to penicillin and frequently also to streptomycin. Overwhelming sepsis was responsible for the patient's death while she was probably on the verge of recovering bone marrow function, as indicated by the monocytosis. The authors stress that all new drugs should be carefully investigated for a possible damaging effect on the hematopoietic functions before their safety is regarded as definitely established.

Quinidine as Cause of Thrombopenic Purpura.—Norcross cites 2 previously reported cases of thrombopenic purpura following administration of quinidine and reports a third case. A woman, aged 66, was admitted to the clinic with a complaint of three attacks of spontaneous bruising and bleeding in the previous seven years. Each attack had been preceded by paroxysmal auricular tachycardia, for which quinidine had been prescribed. A severe episode had occurred five weeks before admission. In accordance with medical advise she had taken 0.37 Gm. (6 grains) of quinidine sulfate when the attack of paroxysmal heart action started and an additional 0.2 Gm. (3 grains) when it had persisted one hour. Several hours later abdominal distress, nausea, weakness and headache developed. These symptoms were followed by petechial hemorrhages into the skin of the extremities and trunk and into the mucous membranes of the mouth. There were numerous ecchymotic areas on the body, epistaxis, hematuria and hematemesis. Later in the same day, there were four convulsions and she became comatose. At that time the platelet count was 85,000, the bleeding time 7 minutes and the clotting time 3 minutes with no clot retraction. After this attack the patient avoided quinidine and there were no more purpuric abnormalities. The author believes that this case represents another example of a rare idiosyncrasy to quinidine resulting in thrombopenic purpura.

New York State Journal of Medicine, New York

50:113-240 (Jan. 15) 1950

SYMPOSIUM: ADULT HEART DISEASE

Differential Diagnosis of Rheumatic and Congenital Heart Disease in Adults. J. G. F. Hiss.—p. 169.
Recent Trends in Hypertensive Heart Disease. M. E. Missal.—p. 173.
*Diagnosis and Treatment of Peripheral Arterial Disease. J. S. Regan.—p. 179.
Mediastinal Emphysema with Spontaneous Pneumothorax. D. R. McKay.—p. 182.
Pneumonectomy for Tuberculous Bronchostenosis. E. N. Packard.—p. 187.
Diaphragmatic Hernia. H. W. Meyer.—p. 190.
Transitory Changes of Refraction in Diabetes Mellitus. J. J. Stern.—p. 195.
*Packing of Mediastinum in Treatment of Hematemesis Due to Esophageal Varices. J. H. Garlock and M. L. Som.—p. 197.
Monaldi Drainage—Valuable Adjunct in Surgical Treatment of Pulmonary Tuberculosis. W. Woodruff and C. G. Merkel.—p. 201.
Decortication of Lung in Nontraumatic Lesions. H. C. Maier and W. W. Fischer.—p. 207.

Peripheral Arterial Disease.—Regan performed 142 sympathectomies on extremities of 99 patients with peripheral vascular disease. Decided relief and increased warming of the foot was obtained in 20 of 21 patients with early arteriosclerosis obliterans. Sympathectomy offers less value in cases of arteriosclerosis obliterans when there is severe pain day and night or obvious gangrene of a digit than when claudication pain is the major symptom. Bilateral sympathectomy is to be preferred to unilateral, since the disease usually involves both legs. Good results were obtained in 20 of 23 patients with Buerger's disease. The patients were young men, but the author believes that nearly every patient with Buerger's disease should be subjected to sympathectomy regardless of the results of preoperative tests. Poorer results should be expected in patients with long-standing Buerger's disease than in those with a shorter history. Complete relief from symptoms resulted in all 15 patients with Raynaud's disease, including 3 with vasospastic phenomena. Preganglionic dorsal sympathectomy is the procedure of choice. Thirteen of 21 patients with post-traumatic dystrophy (causalgia) obtained decided relief, while slight or no relief occurred in the remaining 8. Seven of these 8 patients were women, suggesting that results in causalgia are better in men. The operations on the lower extremity were attended with greater success than were those on the upper extremity. Only temporary relief was obtained in 5 patients with scleroderma.

Hematemesis Due to Esophageal Varices.—Garlock and Som used gauze packing of the mediastinum in 5 men and 2 women between the ages of 21 and 62 and a child aged 2½ years with hematemesis caused by esophageal varices. The packing operation takes advantage of the communicating system at the cardia between the portal and caval circulations. The authors believe that the establishment of a new periesophageal plexus will reroute the portal blood from the submucosal varices to the new plexus, mainly because of the difference in pressures in the portal system and the caval circulation. The direction of flow is from a higher to a much lower pressure area. It is because of this fundamental physiologic fact that mediastinal packing is proposed. In the first of the authors' patients treated with packing of the posterosuperior mediastinum there had been no further bleeding for eight years. The second patient so treated did not have a recurrence of the previously severe hematemesis for four years. The third patient had one episode of bleeding two weeks after leaving the hospital but had shown steady improvement since then for nearly two years. The procedure failed in 2 patients. In 2 patients the packing operation was extended to include packing of the entire posterior mediastinum from the arch of the aorta to the diaphragm through a right transpleural approach, which was performed as a second stage in selected cases. Evidence in the authors' cases indicates that a periesophageal collateral circulation develops after the packing operation. When subsequent hematemeses occur, they are not as severe or profuse as previously, indicating that some of the venous load has been taken from the submucosal varicose network. Mediastinal packing in one or two stages should be carried out before one considers the more extensive and complicated venous shunt procedures.

Northwest Medicine, Seattle

49:1-76 (Jan.) 1950

Use of Cardiac Catheterization in Medical Practice. D. M. Green, A. D. Johnson, W. C. Bridges and others.—p. 27.
Remote Effects of Hypertension in Pregnancy. R. C. Benson.—p. 29.
Helpful Hints for Everyday Practice. A. C. Jones.—p. 33.
Vocational Rehabilitation: As Viewed by Industrial Physician. C. M. McGill.—p. 34.
Repair of Female Urethra. A. F. Lee.—p. 35.
Postoperative Wound Disruptions at Sacred Heart Hospital: Report of Five-Year Study. C. H. Phetteplace.—p. 38.
Human Toxoplasmosis: Family Case Study. J. T. Robson.—p. 42.
Treatment of Enuresis. C. D. Goodhope.—p. 43.
Origin and Development of Northwest Medicine. C. A. Smith.—p. 45.

Oral Surgery, Oral Medicine & Oral Path., St. Louis

3:1-144 (Jan.) 1950. **Partial Index**

Principles and Technique of Exodontia. F. W. Rounds.—p. 3.
Biochemical Factors in Possible Developments of Malformations of Oral Tissues, Especially Cleft Palate and Harelip. D. C. Lyons.—p. 12.
Relieving Pain Caused by Dentures. G. H. Drury.—p. 31.
Bowen's Disease of Mucous Membrane of Mouth: Review of Literature and Presentation of Six Cases. R. J. Gorlin.—p. 35.
Local Anesthetic Solutions: Their Toxicity and Treatment. E. C. Dobbs and M. I. Kader.—p. 52.
Periapical Roentgenography as Applied in Children. M. Lozier.—p. 58.
Partial Anodontia: Brief Review and Case Report of Multiple Familial Incidence. D. J. Kennedy.—p. 63.

Virginia Medical Monthly, Richmond

77:53-104 (Feb.) 1950

Total Colectomy for Benign Conditions—with Consideration of Anal Ileostomy with Sphincter Preservation. M. M. Ravitch.—p. 55.
Fever: Common Symptom in Carcinoma of Stomach. D. A. Berlin and W. B. Porter.—p. 59.
Relation of Pituitary-Adrenal Function to Rheumatic Diseases. G. S. Grier III.—p. 66.
X-Ray Therapy of Non-Malignant Conditions. P. W. Ronan and S. H. Macht.—p. 71.
Correlation of Appendicitis and Oxyuris Vermicularis. C. L. Velkoff.—p. 75.
Anaplastic Carcinoma of Lung with Metastasis to Spinal Cord—Case Report. R. L. Waddell.—p. 77.
Efficacy of Punch-Biopsy of Liver. L. E. Meiselas.—p. 79.

FOREIGN

An asterisk (*) before a title indicates that the article is abstracted. Single case reports and trials of new drugs are usually omitted.

Brain, London

72:265-486 (Sept.) 1949. **Partial Index**

Study of Efferent Connexions of Frontal Lobe in Human Brain After Leucotomy. M. Meyer.—p. 265.
Relative Sympathetic Contribution to Individual Roots of Brachial Plexus in Man. S. Sunderland and G. M. Bedbrook.—p. 297.
Adequate Stimuli (with Special Reference to Cutaneous Nerves). J. H. Parsons.—p. 302.
Sensation and Volition. W. Gooddy.—p. 312.
Hereditary Ataxia with Optic Atrophy of Retrobulbar Neuritis Type, and Latent Pallido-Luysian Degeneration. M. Andre-Van Leeuwen and L. Van Bogaert.—p. 340.
Progressive Fibrinoid Degeneration of Fibrillary Astrocytes Associated with Mental Retardation in Hydrocephalic Infant. W. S. Alexander.—p. 373.
*Subacute Combined Degeneration of Cord: I. Response to Liver Extracts. II. Trials with Vitamin B_{12}. Appendix: Quantitative Method of Assessing Neurological Status. C. C. Ungley.—p. 382.
Spontaneous Electrical Activity of Human Thalamus. D. Williams and G. Parsons-Smith.—p. 450.

Liver Extracts and Vitamin B_{12} in Degeneration of the Cord.—Ungley gives an account of attempts to determine the nature of the agent in liver which is effective in subacute combined degeneration of the cord. These culminated in successful trials with a red crystalline antipernicious anemia factor, vitamin B_{12}, one of the red pigments contained in Lester Smith's less pure earlier material. Eight patients with subacute combined degeneration were studied by the quantitative method described in the appendix to this paper; 2 were affected slightly, 2 moderately and 2 severely. The first 4 patients, who were given the less pure material initially, have been treated for fourteen to nineteen months, for the past thirteen of which they have received the pure substance. The remaining 4 patients, treated for nine to thirteen months, received red crystalline material from the outset. Three of the 5 patients given transfusions noted a diminution of paresthesia, but apart from this none showed improvement and 1 became worse. The improvement observed after vitamin B_{12} therapy was compared with the "expected" improvement based on treatment of 44 patients with liver extract. Four of the 8 patients exceeded the expected rate of improvement, 2 attained it and 2 fell just short of it. Vitamin B_{12} is therefore as effective as liver extract not only in pernicious anemia but also in subacute combined degeneration of the spinal cord. Except perhaps for patients who have become sensitized to some impurity in liver fractions, the pure substance has no advantage over liver extracts, particularly if their potency is determined clinically and microbiologically and expressed in terms of micrograms of vitamin B_{12}. Weekly doses of 40 micrograms or their equivalent in liver extract are usually adequate in the first six months, with half these amounts for maintenance thereafter. At the least sign of relapse, however, or if intercurrent infection should supervene, dosage should be increased until complete arrest of the neurologic condition is assured.

Edinburgh Medical Journal

56:509-572 (Nov.) 1949

Freedom of Thought in Science. F. W. Jones.—p. 509.
On Depression. T. A. Munro.—p. 530.
Surgical Practice in Scandinavia: Some Impressions of Recent Visit. M. R. Ewing.—p. 544.
*Acute Ischaemia of Lower Limb as Complication of Transfusion with Plasma. H. A. F. Dudley.—p. 557.

Acute Ischemia of Limb Following Plasma Transfusion.—Dudley reports that a boy aged 20 months was admitted to the hospital three hours after sustaining a 40 per cent body surface scald involving the head, neck, upper limbs and trunk. He was in severe shock: a plasma transfusion was started by cutting down on the right internal saphenous vein, 4 cm. above the medial malleolus. The child's blood pressure and hemoglobin were satisfactorily maintained during the initial stages of therapy, which included the application of pressure dressings. Twenty-three hours after the injury he was restless and his color was poor, in spite of satisfactory blood pressure; the transfusion was running well, but the right foot was cold. One hour later, coincident with a slight fall in blood pressure and a further deterioration in the general condition, the capillary circulation became sluggish, a cyanotic color developed and arterial pulsation in the foot was absent. The popliteal pulse could not be felt in either leg but both femoral pulses were present. The drip was transferred to the other leg, but the child continued to deteriorate and died three hours later. Acute ischemia associated with intravenous transfusion is rare. Two cases have been described following forced plasma transfusion in infants, but in these intra-arterial thrombus seems to have existed. In the present case four possible mechanisms can be suggested to account for the acute ischemia: (1) massive venous thrombosis; (2) retrograde arterial obstruction through large arteriovenous anastomoses; (3) pressure occlusion of the blood supply, and (4) arterial spasm. The author suggests that arterial spasm was most likely the cause in this case.

Journal of Pathology and Bacteriology, Edinburgh

61:319-498 (July) 1949. **Partial Index**

Hepatic Changes in Young Pigs Reared in Cold and Damp Environment. J. M. Naftalin and J. W. Howie.—p. 319.
Effect of Penicillin on Tubercle Bacillus: Tubercle Penicillinase. C. N. Iland and S. Baines.—p. 329.
Immunisation of Mice Against Group-B Streptococci by Intraperitoneal Inoculation of Living Cultures Combined with Penicillin. I. H. Pattison.—p. 337.
Bacteriological Examination of Faeces. G. T. Cook and R. Knox.—p. 353.
Craniopharyngioma or Para-Pituitary Adamantinoma (Erdheim's Tumour). W. Walker.—p. 359.
Nephroblastoma Occurring in Adult Life. H. A. Sissons.—p. 367.
Experimental Pulmonary Oedema of Nervous Origin. G. R. Cameron and S. N. De.—p. 375.
Identification of Clostridium Oedematiens and Experimental Investigation of Its Role in Pathogenesis of Infectious Necrotic Hepatitis ("Black Disease") of Sheep. S. Jamieson.—p. 389.

Medical Journal of Australia, Sydney

2:829-864 (Dec. 10) 1949. **Partial Index**

*Treatment of Neurosyphilis. E. Susman.—p. 829.
Scope of General Practice. R. G. Quinn.—p. 834.
Ante-Partum and Post-Partum Haemorrhage. W. K. McIntyre.—p. 836.
Closed Head Injury: Modern Conceptions and Their Influence on Treatment. R. S. Hooper.—p. 840.

Treatment of Neurosyphilis.—Susman stresses the importance of the examination of the cerebrospinal fluid in the diagnosis of neurosyphilis, citing several cases in which the correct diagnosis was missed because this examination was omitted. Administration of tryparsamide is useless, and arsenic and bismuth compounds are obsolescent. If penicillin is used as the only treatment, a standard course is 9 to 12 million units, spread over two weeks. No form of neurosyphilis requires intrathecal administration of penicillin. Inadequate treatment is an error. No patient should be pronounced Wassermann fast until he has had repeated courses over a period of two years. Herxheimer reactions should be ignored. This term does not embrace penicillin rashes or other evidence of sensitivity to the drug. The treatment of choice for neurosyphilis is the combination of penicillin and malaria. The fever therapy should be given two or three days before starting the penicillin therapy. It seems reasonable to treat residual psychoses by shock therapy.

South African Medical Journal, Cape Town

23:971-986 (Dec. 3) 1949

Lamellar Corneal Grafts. S. Etzine.—p. 971.
*Wood Dust as Inhalant Allergen: Bronchial Asthma Caused by Kejaat Wood (Pterocarpus Angolensis). D. Ordman.—p. 973.
Epilepsy: III. Surgical Treatment. J. F. P. Erasmus.—p. 977.

Wood Dust as Cause of Asthma.—Ordman reports that asthma developed in a cabinet maker as the result of inhalation of the dusts of several African woods, including kejaat (Pterocarpus angolensis). The man, aged 39, had been working with woods since he was 14 years of age. His asthmatic attacks began when he started to handle kejaat wood. Previously he had worked with mahogany, walnut, teak, oregon, deal and pine. Kejaat is an attractive brown, durable wood, which grows in the Transvaal. The patient said that within one-half hour of being in contact with kejaat he experienced tightness in the chest and difficulty in breathing with cough and considerable sneezing. An intradermal test with kejaat proved positive, although

scratch tests with the same substance proved negative. Desensitization to the wood was carried out by the intradermal method. Relatively few injections of extract of kejaat wood produced rapid relief, and further injections maintained the patient in an asthma-free condition although his working conditions remained unchanged. This case and another case previously described indicate that with the therapeutic use of specific desensitizing wood extracts the prognosis is good.

Annales de l'Institut Pasteur, Paris

77:643-790 (Dec.) 1949. **Partial Index**

Microculture of Kochs' Bacillus on Slides in Human Blood; Use of Preserved Blood for Determination of Streptomycin Resistance. E. Bernard and B. Kreis.—p. 653.
Differentiation of Embryonic Nervous Tissue in Culture on Plastic Membranes. W. P. Wei and G. Barski.—p. 674.
Research on Mode of Action of Sulfone Compounds: I. Bacteriostatic Activity In Vitro. F. Boyer, N. Rist and M. Saviard.—p. 680.
*Prevention of Phenolic Shock During Antirabic Treatment: Importance of Varying Site of Injections. H. Marneffe and H. Seys.—p. 744.

Prevention of Phenolic Shock During Antirabic Treatment.—Marneffe and Seys observed an untoward reaction to antirabic treatment in 13 of 265 persons. The reaction had the character of phenolic shock in 5 of the 13. Two rabbits were treated with phenolated antirabic vaccine, the same site being injected daily. A sudden generalized clonic and tonic crisis resulted in syncope and death within two to three minutes after the nineteenth and twenty-second injection, respectively. A third rabbit which received a long series of injections with the same vaccine, but at various sites, remained unharmed. The generalized clonic and tonic crisis could not be produced in rabbits given antirabic vaccine which was not phenolated. This crisis was interpreted as similar to phenolic shock in man. The crisis was not produced in rabbits given injections with an aqueous 5 per cent solution of carbolic acid in the same dose and at the same time as the phenolated vaccine. The repeated injections of the phenolated vaccine at the same site seemed to have caused the death of the experimental animals. Twelve sites, on the abdomen, flanks and back, were used for repeated series of twelve antirabic injections in 3,000 persons from November 1946 to April 1949, without a single instance of phenolic shock.

Deutsche medizinische Wochenschrift, Stuttgart

74:1453-1484 (Dec. 2) 1949. **Partial Index**

Clinical Aspects of Postwar Endocarditis and Their Evaluation. K. Spang and A. Gabele.—p. 1453.
Syndrome of Latent Jugular Phlebitis. O. Meyer.—p. 1456.
*Clinical, Epidemiologic and Serologic Observations on Q Fever in Northern Württemberg During 1948-1949. F. Freygang.—p. 1457.

Q Fever in Northern Württemberg.—Freygang reports an epidemic of Q fever in the neighborhood of Stuttgart in Northern Württemberg, Germany, from November 1948 to May 1949. Seventy-two persons were affected during the first wave of the epidemic, in November and December 1948. Thirty-four of the 72 patients presented the clinical picture of pneumonia, confirmed roentgenologically. The incidence in men was twice that in women. The youngest patient was aged 6 years and the oldest 72. Approximately the same number of cases were reported during the second wave of the epidemic, in April and May 1949. The incubation period varied from eight to twenty-one days. A prodromal stage with weakness and discomfort for two and rarely for three to six days was followed by rapid rise of temperature, up to 104 F., continuing for five to ten days. Lysis occurred within three to five days. Relative bradycardia and pronounced hypotonia were frequently observed. Lymphocytosis up to 60 and 80 per cent with a normal total leukocyte count was a noteworthy observation. There was a prolonged convalescence period. A cell increase in the cerebrospinal fluid associated with pyramidal symptoms was observed in a single instance only. These observations and the occasional instances of cervical pain with slightly positive Brudzinski and Kernig signs are manifestations of the neurotropic characteristics of Rickettsia burnetii. Complement fixation tests performed in 2 different laboratories in the United States were positive, while those performed in a Swiss laboratory were negative. Animal experiments demonstrated that the causative agent could be transmitted to guinea pigs with the fluoride-blood of a patient with recent fever. Immunity experiments were likewise positive. Sulfonamide compounds and penicillin proved ineffective. All patients recovered except 1 patient, aged 66, who died from heart failure. Prognosis as a rule is favorable.

Minerva Medica, Turin

40:751-774 (Nov. 24) 1949. **Partial Index**

*Fatal Toxic Encephalitis Due to Streptomycin. D. Campanacci.—p. 751.

Fatal Toxic Encephalitis Due to Streptomycin.—Campanacci reports a 35 year old woman who was receiving intramuscular injections of streptomycin for the treatment of pleurisy. She received 1 Gm. of the drug daily in three fractional doses for nine consecutive days. Symptoms of acute encephalitis appeared on the tenth day, one hour after administration of the first dose. The patient died three days later. This is the second case of fatal encephalitis caused by streptomycin observed by the author. Both patients complained three or four days before the appearance of encephalitis of nausea, vomiting, dizziness, noises, fatigue and depression. The neurotropic effects of the drug are particularly likely to manifest themselves in persons with renal or hepatic insufficiency and in patients who had received penicillin or sulfanilamide a few weeks before the administration of streptomycin. The appearance of mild toxic symptoms which indicate nervous intoxication is an indication for discontinuation of streptomycin and immediate administration of dextrose in large doses, of vitamins B and C and cardiac tonics. Streptomycin therapy in the course of penicillin or sulfanilamide therapy is not desirable except where the combination of the two is definitely indicated.

Revista Brasileira de Medicina, Rio de Janeiro

6:727-782 (Nov.) 1949. **Partial Index**

*Indications for Shock Therapy. J. Leme Lopes and L. Robalinho Cavalcanti.—p. 727.

Indications for Shock Therapy.—According to Leme Lopes and Robalinho Cavalcanti convulsion therapy is indicated in the melancholia type of maniac-depressive psychosis, in involutionary melancholia and in the depressive states of presenile psychoses. Electroshock should be used preferably, except in the depressions of presenile psychoses, in which pentamethylenetetrazol (metrazol®) has the advantage of being a convulsant agent and also a powerful cardiovascular drug. Insulin therapy is indicated in the treatment of schizophrenia. If it does not produce favorable results, it should be combined with convulsant therapy. Shock therapy is contraindicated in psychoneuroses.

Ugeskrift for Laeger, Copenhagen

111:1443-1466 (Dec. 22) 1949

*Diplomycin: A New Antibiotic; Preliminary Report. B. Viking.—p. 1443.
Lesion Befalling Lumberjacks. O. Raagaard.—p. 1450.
Isolation of Three Virus Strains of Coxsackie Group from Patients with Meningeal Symptoms. Preliminary Report. H. von Magnus.—p. 1451.

Diplomycin, a New Antibiotic.—Viking reports that since July 1949 diplomycin, a component derived from a Diplococcus isolated by Noster in 1945, has been used in the surgical clinic of Aarhus Kommunehospital in the treatment of 150 patients with different infectious disorders. Diplomycin exerts a pronounced antibacterial action on gram-positive and gram-negative micro-organisms and on tubercle bacilli. The antibiotic effect is ascribed to secretion products of the Diplococcus. Bacteria do not become resistant to diplomycin. It is effective against bacteria which have become resistant to penicillin and streptomycin. Its toxicity is slight. Applied in ointment, diplomycin exerted a notable effect on chronic ulcers of the leg and other localized infections. The clinical effect of intravenous injections of diplomycin filtrates in infections such as abscesses, mastitis and osteomyelitis was often equal to that attained with penicillin. In Bacillus coli infections of the urinary tract diplomycin was sometimes as effective as streptomycin and sometimes superior to it, without the latter's grave side effects. The results of tests of diplomycin in the treatment of pulmonary tuberculosis are said to be promising.

Book Notices

THE REVIEWS HERE PUBLISHED HAVE BEEN PREPARED BY COMPETENT AUTHORITIES AND DO NOT REPRESENT THE OPINIONS OF ANY OFFICIAL BODIES UNLESS SPECIFICALLY STATED.

An Introduction to the Study of Experimental Medicine. By Claude Bernard. Translated by Henry Copley Greene, A.M. With an Introduction by Lawrence J. Henderson, Professor of Biological Chemistry, Harvard University, Boston. Cloth. $3. Pp. 226. Henry Schuman, Inc., Publishers, 20 E. 70th St., New York 21, 1949.

This book was written by Bernard at that period of his scientific career when grouping of facts and theorizing began to take precedence over noting of details. Bernard's outlook in this book is biologic and philosophic. Medicine has passed through the empiric, the systematic, the nosologic and the morphologic stages and has now entered the experimental stage. Bernard envisioned physiology as the foundation of experimental medicine and a larger part of biology. He was superior to his teacher Magendie, as well as to the great Bichat, according to Paul Bert, his pupil and successor to the chair of general physiology at Sorbonne, because he was aware from the beginning of the endless multiplicity of unknown data in physiology and their subordination to the general laws of matter and their obedience to the experimental method. "If a comparison were required to express my idea of science of life," says Claude Bernard, "I should say that it is a superb and dazzlingly lighted hall which may be reached only by passing through a long and ghastly kitchen."

Part 1 of the book deals with experimental reasoning. "The object of the experimental method is to transform an a priori conception, based on an intuition or a vague feeling about the nature of things, into an a posteriori interpretation founded on the experimental study of phenomena." "The freedom which experimenters maintain is founded on philosophic doubt." Further, Claude Bernard states "in scientific education, it is very important to differentiate between determinism, which is the absolute principle of science, and theories, which are only relative principles to which we should assign but temporary value in the search for truth."

Part 2 deals with experimentation with living beings. The idea expressed in this chapter is that there never will be a science of medicine as long as the explanation of pathologic and the explanation of normal, vital phenomena are separated.

In part 3 the author discusses application of the experimental method to the study of vital phenomena. This is probably the most interesting part of the book. The author describes some of his own experiments solely for the purpose of demonstrating the ways of experimentation. Among the experiments cited are those of the study of the curare poisoning, carbon monoxide poisoning, the epochal discovery of animal glycogenesis and the production of artificial diabetes in animals by puncture of the floor of the fourth ventricle.

The place of Claude Bernard in physiology is too well known to require comment. The volume belongs with the classics in medical and biologic literature. The philosophy expounded here is the very embodiment of the credo of the experimenter. The volume should be included in the education of the medical student and in the library of every practitioner of medicine.

Prinzipien des Lebendigen: Eine Studie. Von O. Eichler. Half-cloth, 9.40 marks. Pp. 99, with 8 illustrations. Georg Thieme, Diemershaldenstrasse 47, (14a) Stuttgart O; Agents for U. S. A.: Grune & Stratton, Inc., 381 4th Ave., New York 16, 1949.

This book offers a discussion of "What is Life?" in the light of recent data of physics, chemistry and cytology. The author writes with an excellent understanding of these subjects, and the result is both scholarly and inspiring. The author finds himself obliged to use many semantically treacherous words like "sick," "precancerous" and "disharmony" (page 67), but his epilogue (page 99) indicates that he is aware of the dangers involved. The book is a significant contribution to philosophy and general biology.

Recent Progress in Hormone Research: The Proceedings of the Laurentian Hormone Conference. Volume IV. Edited by Gregory Pincus. Committee on Arrangements, R. W. Bates, et al. Cloth. $8.80. Pp. 529, with illustrations. Academic Press, Inc., 125 E. 23rd St., New York 10, 1949.

This volume of an important series of contributions on endocrine physiology contains the papers and discussions presented at the Laurentian Hormone Conference held at Franconia, N. H., in September 1948. The same high standards that have characterized the previous volumes in this series are maintained in the present volume.

The first section, dealing with hormone metabolism, consists of five papers, one a previously unpublished paper presented at the 1944 conference, on the metabolism of progesterone, estrogens and androgens. G. F. Marrian ably discusses conversion of progesterone into pregnanediol. His work indicates that only a small proportion of administered progesterone is excreted in the urine as pregnanediol. He suggests lines of attack for determining the metabolic fate of the major fraction of progesterone.

Heard and Saffran consider the various avenues of excretion of estrogens, pointing out the importance of biliary and intestinal excretion. Although their technic of using radiohalogenated estrogens may be open to question, their methods and data are of considerable interest. Samuels similarly considers the metabolism of androgens, particularly by the liver, and shows that the liver contains enzymes capable of converting testosterone into compounds not containing an unsaturated ketone structure or a ketonic group on carbon-17. He believes that the formation of 17-kestosteroids is an intermediary step in at least one metabolic pathway.

Of particular interest to clinicians is Segaloff's discussion of the activity and metabolism of estrogens. He points out forcefully the inadequacy of estimations of estrogenic potency on the basis of control of menopausal symptoms.

The second section of the volume includes five papers on the role of hormones in tissue and body metabolism. These papers are of great importance, since considerable light is thrown on the mechanism of action of adrenal cortex steroids, thus offering clues to explain their effects in rheumatoid disease and other chronic metabolic disorders. The problem of antihormones is discussed briefly, and it is pointed out that prolonged administration of steroids does not lead to antihormone formation. Those substances producing antihormones are generally of a protein nature, i. e., pituitary hormones, insulin and possibly parathyroid hormone. Of particular importance to clinicians using cortisone and pituitary adrenocorticotropic hormone (ACTH) is the paper by Thorn and Forsham on metabolic changes in man following adrenal and pituitary hormone administration.

An intriguing section on neurohumeral-hypothalamic relationships contains three papers of interest to the endocrinologist and the neuropsychiatrist. The discussion of adrenal function in mental disease by Pincus, Hoagland, Freeman and Elmadjian throws considerable light on the bizarre mental disturbances seen after prolonged administration of cortisone and ACTH. Of great interest are the data suggesting that certain patients with schizophrenia may have a block to adrenal cortex responsivity because of a lack of normal central nervous stimulation as a result of stress, a lack of pituitary activation or a failure of adrenal cortex secretion. They suggest interesting lines of investigation to elucidate this problem.

The last section of the volume is devoted to thyroid physiology and function. Extensive use of radioactive iodine has aided materially in determining the precise metabolic pathways of iodine and thyroid hormone.

This volume, like its predecessors, is unique in presenting the lengthy discussions following each formal paper. These discussions serve to amplify and extend the data in the formal papers, and the discussants are all well qualified in the fundamental aspects of endocrinology. These annual volumes should be read by every worker in the field of endocrinology, whether he is interested in fundamental laboratory investigations or in the clinical aspects of endocrine disease. With the growing recognition of the role of hormones in mental disturbances, chronic diseases and metabolic disorders, internists, neuropsychiatrists and pediatricians will find much useful information in these carefully edited reports.

Vitamins and Hormones: Advances in Research and Applications. Volume VII. Edited by Robert S. Harris, Professor of Biochemistry of Nutrition, Massachusetts Institute of Technology, Cambridge, Mass., and Kenneth V. Thimann, Professor of Plant Physiology, Harvard University, Cambridge, Mass. Cloth. $7.80. Pp. 488, with illustrations. Academic Press, Inc., Publishers, 125 E. 23rd St., New York 10, 1949.

The seventh annual volume of this series of reviews on selected topics in vitamin and endocrine research follows the pattern of previous editions. As in any book in which the various chapters are contributed by different authors, the articles are variable in quality. On the whole, however, the subjects are presented adequately and fairly.

The first review deals with the controversial subject of vitamin P. The authors open their discussion by defining what is meant by capillary permeability and capillary resistance; a lack of appreciation of the difference between these concepts has been responsible for much confusing and uncritical work. The chemistry and pharmacology of the various substances having vitamin P activity—citrin, hesperidin and the flavonoids—are discussed. Although the authors are inclined to overemphasize the clinical importance of vitamin P, they have performed a useful service in bringing together in a comprehensive article the world's literature on the subject.

The second review, on stereoisomeric provitamins A, deals largely with chemical and bioassay technics for identification and for following the conversion of the provitamins into the active vitamin A. This review will be of interest chiefly to biochemists.

The physiology of thiamine is the subject of an extended discussion in the third article in this volume. The complex relationships between carboxylase, cocarboxylase, thiamine and protein, fat and carbohydrate metabolism are ably elucidated. Much of this work is still speculative, but the author advances an attractive hypothesis regarding the role of thiamine in physiologic processes which meets the facts as they are now known.

Nicotinic acid in amino acid metabolism, particularly in its relation to tryptophane, is presented in a short review. Further insight into the pathologic physiology of pellagra is afforded by this discussion.

The review on diet and aging is an intriguing and stimulating presentation of a subject of great importance. The evidence of the role of diet in the aging process is controversial and, at times, contradictory. This review is a masterly presentation of evidence on all sides of this question and critical analysis. Anyone interested in the subject of geriatrics can read it with profit.

The review on the vitamin requirements of the growing rat will be of interest to workers in experimental nutrition, but most of the material reviewed should be familiar to them. How applicable these studies are to human nutrition appears to be problematic. A companion review on the vitamin requirements of the guinea pig is also presented.

The second section of the book, dealing with hormones, begins with a review on the chemistry of the gonadotropic hormones. The question of nomenclature is adequately discussed, and it is recommended that the old term "leuteotropic hormone" be reserved for the lactogenic hormone, the latter term being preferable. The term "luteinizing hormone" would be better replaced by "interstitial-cell-stimulating hormone," since, in addition to initiating the formation of the corpus luteum, it also stimulates seminiferous tubules and interstitial cells in the male. The chemical nature and physiologic action of the gonadotropins from various sources form the principal topic of review. A special review on the chemistry and physiology of the lactogenic hormone follows the more general review.

The highlight of the whole volume is the splendid review of infra-red spectrometry applied to steroid structure and metabolism, prepared by Jones and Dobriner. In a logical manner, the stereochemistry of the steroids is discussed with extraordinary clarity. The highly complex problem of the relationship of structure to infra-red spectrometry is discussed with such clearness and with such admirable use of structural formulae as to make this review a suitable textbook for all workers in this field.

A brief review of alloxan diabetes is adequate to cover this special subject. A short review on the chemistry of the hormones of the posterior lobe of the pituitary gland is followed by a longer one on the actions of these hormones and their effect on the circulation and the secretion of urine. A major portion of the discussion deals with the circulatory action of these agents, something that has long needed an adequate review.

Although both the vitamins and the hormones are metabolic agents, it seems curious to include reviews on these two subjects in one volume. In general, those interested in the vitamins will not be particularly interested in the reviews on hormones, and vice versa. Since both subjects are developing rapidly, it might be wiser to separate these reviews into two volumes and provide wider coverage of the subject matter. Notwithstanding this criticism, these annual volumes are well worth study by workers in these fields.

Oral Bacterial Infection: Diagnosis and Treatment. By Lyon P. Strean, M.Sc., Ph.D., D.D.S., Director of Research Novocol Chemical Mfg. Co., Inc., Brooklyn, N. Y. Cloth. $5.50. Pp. 185, with 57 illustrations. Dental Items of Interest Publishing Company, Inc., 2911-23 Atlantic Ave., Brooklyn 7, N. Y.; Henry Kimpton, 26 Bloomsbury Way, London, W.C. 1, 1949.

The discussions of the various bacterial groups and infections which are covered in this book are incomplete and frequently marred by erroneous or obsolete information. Few periodontists will agree with the statements to the effect that Vincent's infection is transmitted from person to person by use of infected towels, toothbrushes, pipes or by kissing or that children from 2 to 10 years and adults from 18 to 25 years are most susceptible to the disease. Actually, most of the cases of so-called Vincent's disease found in children have been demonstrated, in recent years, to be forms of herpetic stomatitis. In view of the advances in chemotherapy, it seems improbable that many internists will agree with the author's opinion that in most cases of actinomycosis the termination is fatal, nor will they agree with the view that "the common cold usually has the pneumococcus associated with it as a secondary invader."

In the brief chapter on antibiotics, many inaccuracies will be noted by even the casual reader. In discussing the peanut oil, beeswax, penicillin preparations, the author states, "one intramuscular injection of this mixture, containing twenty thousand units, will maintain a satisfactory blood level for twenty-four hours."

In the paragraph devoted to premedication of dental patients for the control of bacteremia the author suggests intramuscular injection of 100,000 units of penicillin, six to twelve hours before extraction and a similar dose administered twenty-four hours after the tooth has been removed. If the author is referring to crystalline penicillin, it would be eliminated well before the expiration of twelve hours after administration, and, if he refers to procaine penicillin or oil wax penicillin preparations, the dosage is inadequate. The purpose of premedication with penicillin is to produce a high and effective blood level of the antibiotic at the time of extraction and for 24 to 48 hours after the extraction.

In this same connection it is stated, "In a period of forty-eight hours, beginning twelve hours before extraction, a total of ninety milligrams of sulfa drug should be consumed." Aside from the fact that the proposed sulfonamide is not identified, it is difficult to see what value 90 mg. of any member of this group could possibly have over a 48 hour period.

In spite of the fact that lesions of the herpetic group constitute an important segment of oral pathology, the discussion covering them is limited to eight lines. The relationship between herpes simplex and aphthous ulcers is ignored, and the fact that the lesions of herpes zoster are confined to an area corresponding to a sensory nerve distribution is not made apparent. The only suggestion for therapy is the unsubstantiated statement that "large doses of vitamin B complex have proved very helpful in the treatment of herpes."

These examples are cited to demonstrate the careless and incomplete handling of factual material which is prevalent throughout the book. In view of these inadequacies, it seems improbable that this publication will serve a useful purpose in either the medical or dental fields.

Multi-Enzyme Systems. By Malcolm Dixon, Ph.D., Sc.D., F.R.S. Four Special Lectures Given to University College, London, in May 1948. Cloth. $1.75. Pp. 103, with illustrations. Cambridge University Press, Bentley House, 200 Euston Rd., London, N.W. 1; American Branch: 51 Madison Ave., New York 10, 1949.

The book is not a catalog of the various enzymes isolated, their functions in metabolism and their properties but deals with two particular multienzyme systems and their interrelationships. The two systems are the hydrogen-transfer or energy-generating system and the phosphate-transfer or energy-utilizing system.

The first chapter, after a brief introduction dealing with certain properties common to all enzymes, is devoted to the manner in which multiple enzyme systems function to generate, store, transfer and utilize energy. The kinetics of enzyme reactions are also discussed. Various enzyme catalyzed reactions are classified as to the mechanism by which they occur.

The second lecture is concerned with enzyme systems and the mechanism involved in the transfer of energy in living matter by "energized bonds." Various examples are again cited to illustrate the reaction mechanism proposed.

The third and fourth lectures contain discussions of factors determining the direction and the extent of enzyme-catalyzed reactions—phenomena which depend on substrate. In the third chapter the author proposes and suggests a method for the arrangement of the various individual hydrogen-transfer reactions in the multienzyme dehydrogenase system depending on the oxidation-reduction potential of each reaction. This he calls the rH scale of oxidation-reduction—a measure of reducing intensity. The methods of measurement of rH, factors affecting the value of rH and rules for obtaining useful information from rH values are discussed. The first part of the last chapter deals with applications of rH data to hydrogen-transfer multienzyme systems. The remainder of the chapter is devoted to the phosphate-transfer sytsem and a discussion of the feasibility of constructing an rP scale depending on the intensity of the various phosphorylation reactions.

The book has a brief index but does not contain literature references since the material for the lectures was gathered from so many sources that it seemed impractical. This does not detract much from the book, since it was not prepared to be used as a reference book but rather to present an over-all picture and some new ideas on multienzyme sytsems. It is interesting reading and contains much previously unpublished material.

The Biology of Mental Defect. By Lionel S. Penrose, M.A., M.D. With a Preface by Professor J. B. S. Haldane, F.R.S. Cloth. $4.75. Pp. 285, with 18 illustrations. Grune & Stratton, Inc., 381 Fourth Avenue, New York 16, 1949.

The subject of mental defects is of wide scientific interest and of economic and social importance. This book presents, in compressed form, a mass of pertinent data concerned primarily with the scientific biologic area. The first half deals with incidence, classifications, physical stigmas, fertility and causes. As for incidence, careful study of the number of mentally defective persons in the community and in institutions in England indicates that they form 3.1 per cent of the country's population. Applied to the United States, this would give 4.3 million, approximately three fourths of these feebleminded and one fourth imbeciles or idiots, a truly serious burden. The principal discussion centers about the genetics of defect and the relative importance of "nature and nurture." The second half details briefly the known facts about various brain and mental disorders; those considered respectively as dominant, recessive or sex linked and those environmentally conditioned. A reader understanding of genetic terminology and formulas is assumed. The final short chapter is on treatment. The statistical data are taken principally from English mental institutions. The excellent list of references comprises some 500 items.

The presentation is precise, orderly, unemotional, judicial and provocative of thought and debate. Perhaps of greatest interest is the discussion of the genetics of intelligence. The author presents data proving that "genes do play an important part, though not an exclusive one, in determining intelligence level. Thus the problem of the threatened decline in intelligence is a real one" (page 121). Because persons with below average intelligence have the largest families, Burt has predicted an intelligence quotient decline of 2 points per generation. The author, unlike the Spartan ruler Lycurgas, sees no social advantage in allowing hopeless idiots to perish. With respect to the predicted decline in intelligence, he takes a dim view of possible gains from eugenics. Indeed, he states that the groups of better intelligence "not only depend on the less scholastically inclined for manual labor, but for replenishment of genic material." The book ends with this statement: "The genes carried by the fertile scholastically retarded may be just as valuable to the human race in the long run as those carried by people of high intellectual capacity." However, a world faced with a plethora of people and of problems does not need more but better people, and the author does not make clear what valuable genes belong especially to those of low intelligence.

The young-minded J. B. S. Haldane, in his preface, attempts to correct a somewhat conservative and do-nothing attitude of the book by urging that discoveries in prevention or treatment now undreamed of might arise from intensive investigations. As regards ethics, he remarks, "Has a hopeless idiot the right to life and care, though he or she is not a rational being nor likely to become one? If so, has a chimpanzee with considerably greater intelligence similar rights and, if not, why not? If not, where are we to draw the line?" Haldane's belief that the book should be read by physicians, social workers and members of Parliament is well grounded.

Applied Anatomy and Kinesiology: The Mechanism of Muscular Movement. By Wilbur Pardon Bowen, M.S. Sixth edition revised by Henry A. Stone, M.S., Associate Supervisor, Department of Physical Education, University of California, Berkeley, California. Cloth. $4.75. Pp. 390, with 234 illustrations. Lea & Febiger, 600 S. Washington Sq., Philadelphia 6, 1949.

The fact that this text has gone through so many revisions since its original publication in 1917 is presumably good evidence that it has pleased the readers for whom it was obviously designed, namely, students of physical education. Part I consists of short general discussions of the skeleton, muscles in general, the nervous system and the mechanical principles of muscular action and a chapter on the complex chemistry of muscle contraction. Parts II, III and IV discuss the muscles of the limbs and trunk and the mechanism of breathing. In these sections a short discussion of the movements of a part of the body is followed by brief statements concerning the origin, insertion and actions of the individual muscles concerned in moving this part. The anatomy so presented is limited but probably adequate for the use for which this book was intended. Apparently these parts of the book have undergone the least revision, and this is reflected in the curious use of a few pre-BNA terms, such as extensor ossis metacarpi pollicis for abductor pollicis longus, the writer apparently believing that these are the modern and preferred terms. Part V is primarily a tabular résumé of the three preceding parts. Part VI, considerably more thorough, discusses posture, walking, running and jumping and the technic of numerous sports and everyday occupations, with an analysis of the muscles concerned in the various movements. The anatomic part of this text is for the most part adequately illustrated with figures taken from textbooks of anatomy, and with photographs showing muscles in action, and the portion on games and sports with photographs of actual games or participants.

Major Problems of United States Foreign Policy, 1949-1950. Prepared by the Staff of The International Studies Group of the Brookings Institution. Cloth. $3. Pp. 492, with 14 maps and charts. The Brookings Institution, 722 Jackson Place, N.W., Washington 6, D. C., 1949.

This volume is the third in a series of annual publications on problems of United States foreign policy, which constitutes a part of The Brookings Institution's broad program of research and education in the field of international relations. This program, inaugurated in 1946, is being carried out by the institution's International Studies Group under the direction of Leo Pasvolsky.

In undertaking the program, The Brookings Institution has two objectives: first, to aid in the development of an informed and responsible American public opinion on foreign policy and, second, to aid in the training of the increasing number of American specialists in international relations that are required today in government, in business and in other agencies operating

abroad. The method used is analysis and interpretation of the major problems that arise in this country's foreign relations in a manner similar to that used by government officials in dealing with policy issues. Since such specialists must come primarily from the colleges and universities of the country, it is clear that if students are given some training in the policy-making process while they are perfecting their general and specialized knowledge they will be more adequately prepared for participation in the conduct of foreign relations.

The technic employed in this volume is based on what may be termed the problem approach. In part I there is a brief description of the world scene—political, economic and military—in the summer of 1949 and an analysis of the position of the United States in world affairs. Part II reviews the main problems of foreign policy with relation to specific problems of several regions, such as Indonesia, Europe and Russia. The book closes with a discussion of three specific problems, American assistance to underdeveloped areas, the problem of Indonesia and that of European economic integration.

Pathology and Surgery of Thyroid Disease. By Joseph L. DeCourcy, M.D., Director, DeCourcy Clinic, Cincinnati, Ohio, and Cornelius B. DeCourcy, M.D. Cloth. Price, $10. Pp. 476, with 94 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1949.

In their thirty years of experience with disease of the thyroid, the authors have evidently arrived at some sound ideas regarding the function and pathology of this organ. This they have presented in a brief monograph, which contains a good many references from the literature. A vast amount has been written about goiter; much of it is no longer valid. The role of iodine is being studied anew with the aid of radioactive isotopes. The addition of new drugs in the management of hyperthyroidism and the diminished frequency of goiter have decreased the need for surgical treatment. Emphasis is now being placed on cancer of the thyroid. This subject is well presented. The relationship of aberrant thyroid tissue and benign metastasizing goiter is described according to modern opinion. The treatment of cancer of the thyroid is difficult, but the management outlined is useful. The value in carcinoma of the radioactive iodine is correctly stated to be doubtful. The use of the isotope as a tracer and in hyperthyroidism is another matter and will undoubtedly increase. The illustrations both of pathologic specimens and of surgical technics are excellent. This is a fine review of the status of our knowledge about the thyroid, with a rational opinion on a controversial and interesting subject.

Hematin Compounds and Bile Pigments: Their Constitution, Metabolism, and Function. By R. Lemberg, Dr. Phil., and J. W. Legge. M.Sc. Cloth. $15. Pp. 749. Interscience Publishers, Inc., 215 4th Ave., New York 3; 2a Southampton Row, London, W.C. 1, 1949.

There has been no single book in the English language on porphyrin compounds and bile pigments to which the interested student and worker could refer. The closest approach has been reviews of certain aspects of the broad field. This volume fills the gap adequately. It is written by men who have had extensive experience in this field of study, and the subject matter was reviewed and checked by many international authorities before publication.

The authors have attempted to summarize the present knowledge for students and to present a reference source for research workers and those interested in detailed information. The emphasis is primarily on biochemical data, but much of it is of interest to clinicians and pathologists.

The introductory chapter is a brief review of the biologic significance, chemical structure, variability and metabolism of pyrrole pigments. The pyrroles are the basic units from which porphyrins and bile pigments are formed. This is followed by a fairly detailed discussion of the physical chemical methods of investigation. There are two chapters on the nomenclature and detailed chemistry of porphyrins and bile pigments. These preface an extensive review of hematin compounds in general and hemoglobin in particular, including the comparative biochemistry and physiology of the latter. This is followed by chapters on hematin enzymes, mechanisms of bile pigment formation, hemoglobin catabolism in its breakdown to bile pigments, hematin and porphyrins in normal and pathologic conditions and the formation of hemoglobin and synthesis of porphyrins in the animal body. The final chapter is a brief discussion of the pyrrole pigments in evolution.

The bibliography carries over 3,000 references. The index is complete and adequately cross referenced. Even if there were available other books in English on this subject, this volume would rate as a necessary addition to the library of interested workers.

An Introduction to Clinical Surgery: Surgical Wherefores and Therefores; a Reasoned Explanation of Surgical Note-Taking. By Charles F. M. Saint, C.B.E., M.D., M.S. Second edition. Cloth. 45s. Pp. 383, with 373 illustrations. Published for The Post-Graduate Press by Juta & Co., Ltd., Cape Town and Johannesburg; Agents in U. S. A.: Stechert-Hafner, Inc., 31 E. 10th St., New York 3, 1949.

This first edition of this book was published in 1945. This edition differs from the first chiefly in the addition of numerous clinical photographs and diagrams, but the text also has been revised.

The subtitle is accurately descriptive of its point of view and content. Its author says one of his main objects is to sidestep the "parrot" type of acquiring knowledge, which he calls "psittacism," and provide knowledge based on reasoned thinking, which is much more lasting and permanent. Accordingly, he quotes no authorities and provides no bibliography but, reasoning from the basic medical sciences, chiefly anatomy, physiology, pathology, and biochemistry, he adds the consensus of clinical technic as developed in his own experience to make the acquisition of diagnostic insight and skill as easy and natural as possible. What emerges is a handy-sized volume of text in the style of Zachary Cope's "The Early Diagnosis of the Acute Abdomen" or Hamilton Bailey's "Demonstrations of Physical Signs in Clinical Surgery," both of which have had immense student appeal in this country.

Although the chief emphasis is where it belongs, on the significance of enlightened history taking, inspection, palpation, percussion and auscultation, adequate but pithy accounts of the use of modern diagnostic instruments and technics are given. The illustrations add greatly to the value of the text because they are generally well chosen and executed, though some show advanced lesions of the spectacular "museum" type and others provide a "foreign flavor."

The chief appeal of the book will undoubtedly be for students seeing surgical cases for the first time, and they will undoubtedly want to take the book with them to the clinic and the bedside, a use for which it is admirably suited. Interns, house officers and practicing surgeons may not wish to consult the volume so openly, because it is obviously elementary, but they will profit by having it around for frequent consultation because it is both informative and readable.

The only nonspecific discussion is in chapters devoted to inflammations, swellings, calculi and fractures. Otherwise, the chapters encompass the body by regions and in specific fashion. There is a short subject index.

Der Arzt in der Krise der Zeit. Von Medizinalrat Dr. Karl Rom. Paper. 11 Swiss francs. Pp. 181, with illustrations. Franz Deuticke, Helferstorferstrasse 4, Vienna 1, 1949.

This book reviews the historical, philosophic and practical aspects of the relation of the physician to society. Some especially interesting historical material relates to the universities of Innsbruck and Graz. The most important parts of the book, however, are those dealing with the organization and operation of plans for public health, group insurance and social security. A section headed "Quo vadis medice?" beginning on page 95, contains a description of conditions of medical education and practice in central Europe today and includes a discussion of euthanasia. On page 140 there begins a section on the work of the physician under socialized medicine, written with frankness and clarity; problems of training, responsibility and remuneration are discussed, and specimen laws and contracts are quoted. These portions deserve translation into English because of their bearing on questions now confronting the people of the United States.

Queries and Minor Notes

THE ANSWERS HERE PUBLISHED HAVE BEEN PREPARED BY COMPETENT AUTHORITIES. THEY DO NOT, HOWEVER, REPRESENT THE OPINIONS OF ANY OFFICIAL BODIES UNLESS SPECIFICALLY STATED IN THE REPLY. ANONYMOUS COMMUNICATIONS AND QUERIES ON POSTAL CARDS WILL NOT BE NOTICED. EVERY LETTER MUST CONTAIN THE WRITER'S NAME AND ADDRESS, BUT THESE WILL BE OMITTED ON REQUEST.

IMMUNIZATIONS BEFORE GOING TO EUROPE

To the Editor:—**What immunization do you consider necessary for a trip to Italy, France, England and Germany? Would you advise a series of typhoid inoculations in a woman 55 who had typhoid as a child? Also, is the intradermal typhoid immunization as good as the subcutaneous?**

Herbert H. Von Gal, M.D., Brewster, N. Y.

ANSWER.—For the trip proposed it is advisable to establish the absence of susceptibility to or to immunize against smallpox, typhoid, typhus and diphtheria. Inoculations for immunization against typhoid should not be necessary for a person who has had the disease. Intracutaneous injections of typhoid vaccine will produce immunity, but it is generally believed that the subcutaneous route should be used. For such an extended journey as the one contemplated, protection against typhus also seems advisable.

RECURRENT PAPILLOMA OF LARYNX

To the Editor:—**A boy 4½ years of age has been treated for multiple papillomas of the larynx for two and one-half years and has been under my care for the last year and a half. A tracheotomy tube has been used constantly. About six months ago he was taken to Stanford University Hospital, where local applications of podophyllin solution were applied to the larynx. The lesions regressed rapidly, and treatment was continued for about six weeks after he returned here. However, as soon as the treatment was stopped the lesions recurred. About one year ago another patch of papillomas developed at the bifurcation of the trachea, and the growth seems to be spreading downward. It is now necessary to do bronchoscopy every four to six weeks to keep the airway clear. Authorities seem to agree that multiple papillomas of the larynx disappear at puberty if the child can be kept alive that long. What status has male hormone therapy for this condition and what are the underlying factors that cause multiple papillomas? Would it be advisable to try hormone therapy on a child 4½ years of age, and, if so, what dosage is suggested? He seems to be healthy otherwise.**

Wells C. Carey, M.D., Eureka, Calif.

ANSWER.—The etiology of papilloma of the larynx is not definitely known. One factor that is known is its persistent recurrence in spite of all methods of treatment that are used. The treatment of this condition by sex hormones has not given satisfactory results. Removal of the papillomatous tissue under direct laryngoscopy by proper forceps appears to be the most satisfactory method available at present. Irradiation in children should never be considered, because of the delicate nature of the laryngeal structures and the possibility of permanent trauma following the irradiation. Tracheotomy in these cases helps prevent sudden closure of the airway and consequent asphyxia; it also may have a definite beneficial effect in inhibiting the growth of papillomatous tissue by putting at rest the laryngeal structures. Several cases have been followed in which definite improvement, i. e., lessening of recurrence of papillomatous tissue, was noted after tracheotomy.

PERIANAL LEUKOPLAKIA

To the Editor:—**A white man of 74 years has a chronic ulcer extending anteriorly from the mucocutaneous border of the anus. This was excised five years ago and recurred one year ago. Biopsy of the ulcer six months ago showed leukoplakia. The ulcer almost healed after the biopsy but is now about as large as it was a year ago. The zone of leukoplakia completely surrounds the anus, although there is only one area of chronic ulceration.**

M.D., Wisconsin.

ANSWER.—While leukoplakia involves the mucosa of the rectum beginning at the mucocutaneous line in relatively few patients, treatment, including excision and radiation, is not completely successful. This lesion in this location has not been known to develop into a carcinoma. Ulceration does occur, and in at least one instance a papillary tumor occurred, which, however, was benign. Excision would seem to be the safest treatment of a leukoplakia that had ulceration in it or from which a papillary growth had developed. If the zone of leukoplakia completely surrounds the anal ring, it can be excised and then the mucosa of the bowel can be excised and resutured to the mucocutaneous line.

DEATH FOLLOWING NARCOTIC ADDICTION

To the Editor:—**I have been called to testify in a case of death where there seems to be some doubt whether the patient died as a result of voluntary withdrawal after a long addiction to codiene and meperidine hydrochloride (demerol hydrochloride®), or whether she died as a result of a large dose of morphine (possibly impure) after ten to fourteen days of partial withdrawal. She was supposed to be intolerant to morphine, and the relatives charge that she died from an overdose of morphine or as a result of an allergic reaction to morphine. It is not known whether the patient received morphine just prior to her death, but the toxicologist reports that traces of the alkaloids were found two years after death and after she was embalmed. The patient died from a cardiac complication about seven hours after the morphine was supposed to have been given.**

J. J. Johnson Jr., M.D., Las Vegas, N. Mex.

ANSWER.—The data contained in the letter are not sufficient to permit a definitive answer. The dose of morphine received by the patient is not stated. There is no information about other medicaments that this patient received on the day when the morphine was administered. There is no statement of the quantity of morphine found at the autopsy other than that traces were present, and there is no information with regard to any pathologic changes found at postmortem examination.

Unless a narcotic addict is suffering from some serious organic disease, death during withdrawal is unusual even after abrupt and complete withdrawal of morphine. Death from withdrawal from either codeine or meperidine or both would be unusual, since the abstinence syndrome from both drugs is mild. The letter also states that the patient had had a "partial withdrawal" of ten to fourteen days. It is assumed that this means that the dosage of codeine and meperidine had been gradually reduced but not completely discontinued over that period of time. In such circumstances the intensity of the abstinence syndrome would be so mild that it would be difficult to attribute the death to withdrawal.

The patient's symptoms prior to death were not those usually seen in acute morphine intoxication, in which coma and respiratory depression are the outstanding features. It therefore seems unlikely that the death was due to acute morphine poisoning. According to Bieter and Hirsch (*Ann. New York Acad. Sc.* **51**:137, 1948) untoward circulatory reactions occasionally follow administration of therapeutic doses of morphine, methadone and meperidine. Such reactions are comparatively rare with morphine and represent the normal risk inherent in the administration of this drug.

The most extensive reference on poisoning by morphine can be found in the book, "The Pharmacology of the Opium Alkaloids," by H. Krueger, N. B. Eddy and M. Sumwalt (*Pub. Health Rep. Supp.* no. 165). This book is probably available in the libraries of all medical schools.

FETAL DEATH FOLLOWING TETANUS ANTITOXIN GIVEN TO MOTHER

To the Editor:—**On the morning of Oct. 2, 1949 I delivered a white primipara aged 20 of a stillborn term fetus. The baby weighed 6 pounds, 5 ounces (2,863 Gm.) and did not seem to be deformed in any way. The cord was of average length, was not knotted or around the baby's neck. The baby gave the appearance of having been dead at least forty-eight hours. The mother had been normal during her antepartum period. She is type A, Rh positive. Her urine and blood pressure were normal, and her weight gain was 16 pounds (7.3 Kg.). At her last antepartum check three days before delivery, the head was low, the baby active, and fetal heart tones of 140 per minute were heard in the left lower abdominal quadrant. She was seen that evening with a puncture wound on her right sole from stepping on a nail. I gave her 1,500 units of tetanus antitoxin after she exhibited no reaction from her intradermal test. I waited twenty minutes to read the test. She began labor about 4 p. m. October 1 and was delivered at 1:25 a. m. October 2. She felt no life the morning after receiving the antitoxin injection. Was tetanus antitoxin the cause of death in this case?** **R. G. Neher, M.D., Shoshone, Idaho.**

ANSWER.—The history fails to supply the necropsy observations of the stillborn fetus as well as other important data, which makes it difficult, if not impossible, to predicate any suggestions concerning the cause of death. In the absence of a necropsy record, no valid justification can be invoked to incriminate the injection of tetanus antitoxin as the cause of fetal death. In this respect, it may be intimated that the negative skin test is of significance, although such an observation does not exclude the possibility of systemic sensitivity. As already stated, a negative skin test merely means that fixed antibodies were not detected in the skin. In view of the information presented, it is the joint opinion of a group to which this problem was submitted that no evidence of a convincing character has been offered to incriminate the tetanus antitoxin.

Presuming that such a verdict is incorrect, one must entertain the following possibilities: 1. Primary toxicity of the tetanus

antitoxin. Such an explanation, while not completely excluded, did not seem plausible. 2. Allergic reactions at the uterine or placental sites, causing premature onset of labor pains or abruptio placentae. These possibilities do not seem likely because the antigen-antibody reaction occurs only at sites composed of delicate smooth muscle components (terminal bronchioles, small arterioles, pulmonary artery, adrenal vessels, perineural vessels and hepatic venules). A structure, such as the placenta or a gravid uterus, with large vessels, would be too resistant to vascular spasm. 3. Fetal anaphylaxis with spasm of the adrenal vessels, the hepatic venules or the pulmonary artery. If one accepts the possibility of fetal anaphylaxis in this case, it remains to explain the different responses of mother and fetus to the same potentially noxious agent, i. e., tetanus antitoxin. The following facts may be cited in reference to an elucidation of this problem: 1. In smallpox, mother and fetus may react in different fashions. (Pregnant women in whom smallpox infection is absent or who are immune, through vaccination or revaccination, or who had mild attacks without any rash, may give birth to an infant with typical variola eruptions or scars of smallpox.) 2. The quantitative factors, in respect to antibody (reagin) and antigen are different for the mother and fetus because of differences in respective body sizes.

In view of the circumstances described, it would appear desirable to induce a state of active immunity in the mother under consideration. In order to avoid any unjustified criticism, this procedure should be instituted during a period when the patient is not pregnant. The dose of 1,500 units in this case was inadequate. The present trend is to employ prophylactic doses of 5,000 to 20,000 units of tetanus antitoxin.

Reference:

Ratner, B.: Allergy, Anaphylaxis and Immunotherapy, Baltimore, Williams & Wilkins Company, 1943.

CHOLESTEROL STONE IN GALLBLADDER

To the Editor:—**A man aged 44 gives a history of intermittent constipation for ten years (irritable colon type). He has never had nausea or vomiting or decrease in appetite. Two months ago as a result of increasing constipation, which lasted about two weeks, he had a roentgenographic examination of the gastrointestinal tract, including barium enema, but it revealed nothing significant. Roentgenography of the gallbladder revealed an apparently normal organ except for the presence of a nonopaque calculus. After a fatty meal to empty the gallbladder the patient noticed a vague, dull, gnawing pain between the shoulder blades which lasted two or three hours. Since then he has had a similar pain without nausea within an hour after some meals. He has not had loss of weight (165 pounds [74.8 Kg.]). His height is 5 feet 9 inches (175 cm.). He has some vague epigastric distress especially after heavy meals and when excessive amounts of fats are taken. In the past he has been prone to eat large amounts of fats and carbohydrates. The foregoing symptoms were not present before the first fatty meal for a roentgenogram. Please outline treatment. Is there evidence to show that some of these calculi disappear with or without a decrease in fat ingestion or with cholagogues? Do any gastric disturbances follow cholecystectomy?**

M.D., New York.

Answer.—It seems evident that this patient has in the gallbladder a solitary cholesterol stone that produces intermittent obstruction and thus interferes somewhat with the emptying of the gallbladder in response to a fatty meal. The epigastric distress in all probability arises as a result of contraction of the gallbladder in the presence of temporary obstruction to the cystic duct as a result of the stone. Such calculi do not disappear spontaneously, nor are they removed by the use of cholagogues or alterations in the diet. Probably this cholesterol stone has appeared in the gallbladder as a result of a metabolic defect rather than infection; however, such stones cause stasis of bile in the gallbladder, and this in turn leads to infection. In the biliary passages, as in the urinary passages, natural resistance to infection is due in large part to the tortuosity of the tubular passageway and to the onward and outward flow of secretion. Conversely, any factor that interferes with the onward flow of secretion, resulting in stasis, permits the growth of bacteria with subsequent invasion of the wall. There are many cases in which a solitary cholesterol stone has remained in the gallbladder for thirty or forty years without seriously interfering with health, but this is not the usual sequence of events. As a result of stasis and infection numerous secondary stones composed of calcium bilirubinate become deposited in the gallbladder, with progressive damage to the gallbladder wall, biliary colic and the other sequelae of gallstones. In view of the exceedingly small risk of cholecystectomy in the hands of well trained surgeons throughout the United States, this operation is the treatment of choice. Cholecystostomy is not indicated in this instance because of the probability of reformation of stones. Gastric disturbances seldom follow cholecystectomy for gallstones.

PURPURA RHEUMATICA

To the Editor:—**A white woman, aged 25 and four months pregnant, has had a purpuric rash for about a year. The rash consists of numerous scattered pale pink to purplish macules, mainly on the feet, ankles and lower part of the legs but at times extending to the thighs. Most of the lesions are discrete, but some are confluent in certain areas, notably at pressure areas such as those where shoe straps cross the feet. The eruption appears and fades at irregular intervals but in recent months has occurred at intervals of several days. On some occasions there has been swelling and tenderness around the ankle joints coincident with the rash. There is usually some subjective pain in the areas of the eruption. She has had nose bleeds and recently oozing from the dental gingivae. Familial history does not elicit any information on the subject. There has not been any exposure to drugs or industrial chemicals associated with these lesions. Seven months ago, because of a recurrent tender mass in the left lower abdominal quadrant, a laparotomy was performed but nothing of consequence found; apparently the mass disappeared during the preoperative interval. She has also consulted an obstetrician and an internist. Examination elicited nothing significant except a doubtfully positive tourniquet test. Blood studies have revealed normal values for red, white and differential blood cells and hemoglobin content, and normal values for thrombocytes, bleeding, coaggulation time and clot retraction time. The eosinophil count on one occasion was 12 per cent. The general opinion is that this is a purpura simplex, perhaps with a Schönlein-Henoch factor. What is suggested for treatment and investigation?**

John W. Bickley, M.D., Waterloo, Iowa.

Answer.—The observations described are characteristic of allergic purpura, sometimes called simple purpura, Schönlein's disease or Henoch's purpura. When the disease is accompanied with arthralgia it sometimes is called Schönlein's purpura or purpura rheumatica. When angioneurotic edema occurs in the bowel, producing the syndrome of partial intestinal obstruction, the condition sometimes is called Henoch's purpura. Since there is no history of exposure to drugs, there probably is an allergy to some food or to one of the organisms in the gastrointestinal tract. As a rule, these patients do not have any tendency to serious bleeding at operation or delivery. A trial of antihistaminic therapy may be worth while. Ascorbic acid and rutin are usually given to such patients, but it is doubtful whether there is enough evidence to establish definitely that these medicaments are of value. Even without therapy the chances are excellent that the woman will not have any more troublesome symptoms than those she now has. Curative therapy consists in finding the offending food by a daily dietary diary or using elimination diets; one must either eliminate this food or desensitize the patient to it. Treatment by this method usually is more troublesome than the disease, and reassurance may be sufficient.

TABETIC PAINS

To the Editor:—**I have a male patient 70 years of age who suffers from tabetic pains in his legs. Is there anything new for the prevention or lessening of these pains?**

M.D., Florida.

Answer.—The treatment of a patient 70 years of age with tabetic pains is not different from the treatment of tabes dorsalis in general. The activity of the neurosyphilis first must be ascertained. Evaluation can be made only by an examination of the cerebrospinal fluid, including the cell count, globulin content and reaction to the colloidal gold and Wassermann tests. Of these, the most important signs of active disease are the cell count and globulin estimation, both simple tests best done by the examiner in his own laboratory. Antisyphilitic treatment is indicated if any signs of specific disease are found. Even if no activity is demonstrated by this means, tabetic pains sometimes may be relieved by this treatment. At present, treatment with intramuscular injections of penicillin has almost totally replaced former types of medication. The results are not much better than when arsphenamine, tryparsamide and malarial or other types of fever therapy were used, but penicillin is much easier to administer, and in most cases treatment is at least equally satisfactory. Some authorities favor the simultaneous use of penicillin and the development of malaria infection to induce fever, but, as was recently pointed out, results of intramuscular injections of penicillin without fever are similar to or better than those following heat therapy. (Dattner, B.; Thomas, E. W., and deMello, L.: Treatment of Neurosyphilis, *J. A. M. A.* **141**:1260 [Dec. 24] 1949). In all cases the active disease as judged by abnormalities in the cerebrospinal fluid should be abolished by penicillin; in about 65 to 85 per cent of the patients lightning pains should be lessened and in some cases eradicated after a full course of either penicillin therapy alone or malaria plus penicillin (Chesney, L. P., and Reynolds, F. W.: Penicillin in Treatment of Neurosyphilis. IV. Tabes Dorsalis, *Arch. Neurol. & Psychiat.* **59**:347-359 [March] 1948).

For the few cases of tabes dorsalis with lightning pains that do not respond to either form of therapy, various forms of treatment have been tried. Some patients have responded to such simple treatment as small doses of a bismuth compound intra-

muscularly in courses of six or eight injections on a weekly basis two or more times a year. Various anesthetic agents or even distilled water have been injected into the subarachnoid space, usually without more than temporary relief. Should the pains be confined to one area for a long period of time so that a spinal root or one or two roots can be identified as the site of the main lesion, cutting of these roots is occasionally justified. However, such an eventuality is unusually rare, and surgical procedures of this type cannot be advised in a patient 70 years of age. This opinion, too, would apply to sympathectomy and other forms of surgical intervention. Dependence should therefore rest on a thorough knowledge of the activity of the process as estimated by a complete examination of the cerebrospinal fluid and the use of penicillin over an appropriate period of time. If this form of treatment is not successful malariotherapy may follow, but intrathecal treatment and spinal surgery should be avoided.

BURSITIS

To the Editor:—**Kindly furnish me with a differential diagnosis between bursitis of the shoulder and tearing or avulsion of the subscapularis (the so-called subcapularis syndrome).** **M.D., Pennsylvania.**

ANSWER.—The distinction between bursitis of the shoulder and tearing or avulsion of the subscapularis tendon or any of the other tendons which make up the rotator cuff (supraspinatus, infraspinatus and teres minor) is one of degree, as all these structures form a part of the working mechanism of the joint. It is doubtful that any important tearing of any of the tendons that make up the rotator cuff could take place without some degree of bursitis, as the floor of the bursa is in immediate contact with the tendon beneath. True bursitis of the shoulder is seldom primary. Long before the bursitis becomes clinically evident, a process of gradual degeneration has been taking place in the tendons about the shoulder joint. Such attrition is brought about by multiple minor traumas with resulting fibrosis and diminution of blood supply. This is usually followed by some degree of calcification in the tendon, which can be seen roentgenographically. Such calcifications may not produce symptoms, and they frequently are found incidentally in roentgenograms of the chest or of the shoulder. If, however, pain and limitation of motion do occur concomitantly with tendon calcification, it means that this calcification is superficial enough to irritate the floor of the bursa or even rupture into it. This will produce a rather sudden onset of increased tenderness and lead to alarming pain and disability.

With sufficient trauma, usually with the arm in abduction and external rotation, actual tearing of any of the components of the rotator cuff may occur. In relatively minor tears of one portion of the cuff, the other portions may take over the duties and only critical examination can determine which portion has been torn. In examining such a shoulder one should visualize the cuff as divided into posterior, superior and anterior segments. The anterior segment, if torn, will not be able to stabilize the humerus so as to permit abduction when the arm is externally rotated. The superior segment will not be able to act with the arm in a neutral rotatory position, and the posterior segment will be deficient in abduction with the arm in extreme internal rotation. If all segments are involved, as in complete cuff tear, no abduction is possible, because no tendon is left to fit the humerus snugly against the glenoid. The writings of E. A. Codman (Shoulder: Rupture of the Supraspinatus Tendon and Other Lesions in or About the Subacromial Bursa, Boston, Thomas Todd Co., 1934) and H. L. McLaughlin (Common Shoulder Injuries: Diagnosis and Treatment, Am. J. Surg. **74**:282-295, 1947) clearly outline this problem, and these are recommended reading for those interested in this subject.

BLEEDING FOLLOWING ONSET OF MENOPAUSE

To the Editor:—**A 57 year old white woman began to experience hot flashes and irregular menses twelve years ago. In the last two years her periods have been infrequent, perhaps three or four times a year, but last month she menstruated for a full week, the quantity being about normal. Many times there is a mere "show" for a day or two. Her hot flashes have persisted; they are helped by use of diethylstilbestrol, but they are not relieved by large doses of estrone. Examination at regular periods has shown no evidence of fibroid or cancer. What is the likelihood of this patient's becoming pregnant? Are there instances of pregnancy at her age?** **M.D., Michigan.**

ANSWER.—A woman who bleeds after the onset of menopause (hot flashes) should receive a diagnostic curettage to rule out cancer of the uterus. It is unlikely that this patient would become pregnant, although pregnancies have been reported in women of this age. Estrogen given for treatment of menopausal symptoms may produce bleeding.

ANTITOXIN GIVEN BEFORE RECEIPT OF LABORATORY REPORTS

To the Editor:—**A boy aged 11 years had a temperature of 99.4 F., acute follicular tonsillitis with large, discrete follicles, ringworm on the right arm, and a blotchy erythema on the neck, groin, knees, ankles, elbows and wrists. The diagnosis was tonsillitis with toxic erythema and ringworm. He was given a triple sulfonamide preparation, 15 grains (0.97 Gm.) every four hours while awake, tyrothricin lozenges every two hours and 400,000 units of penicillin intramuscularly. The next day his temperature was 101 F. The exudate had spread and was confluent over both tonsils. The lymph nodes in the anterior cervical triangles were swollen and tender. The child had been immunized against diphtheria in 1939 at the age of 10 months and had a negative Schick test at the age of 16 months. He received a booster diphtheria-tetanus toxoid inoculation at 9 years of age and another booster inoculation two months before the present illness. Smears were stained in my office using Albert's stain. It was believed that diphtheria organisms were present and a clinical diagnosis of diphtheria was made. Without waiting for the laboratory reports, I gave the patient 20,000 units of antitoxin after ophthalmic and skin tests were negative. Twenty-four hours later his temperature was normal and the membrane was beginning to separate from the tonsils. However, it was still tenacious and confluent. The lymph nodes were much less tender and swollen. Convalescence was uneventful. Two laboratories reported that cultures were negative. The head of one of these laboratories holds that a diagnosis of diphtheria cannot be made without the confirmatory evidence of a culture exhibiting growth of Corynebacterium diphtheriae. I cannot agree with this view. Can a diagnosis of diphtheria be made despite negative cultures? Should antitoxin be withheld from a patient exhibiting a confluent, adhesive membrane until positive cultures can be obtained?** **C. L. Concklin, M.D., Corpus Christi, Texas.**

ANSWER.—Occasionally cultures from a diphtheria patient may be reported as negative. In such circumstances there may be an abundance of necrotic tissue (membrane). However, a repetition of cultures should disclose the organism. The evidence presented in the query is strongly against a diagnosis of diphtheria. Nevertheless, diphtheria antitoxin should never be withheld when a clinical diagnosis of diphtheria seems apparent. In the past diphtheria accounted for many deaths because administration of antitoxin was delayed until a laboratory diagnosis was made.

DETERMINATION OF SERUM PROTEINS

To the Editor:—**When the falling drop method is employed for the determination of serum proteins, is it permissible to use serum discolored to a dark burgundy by laking of a small part of the clot? If not, will any of the more common laboratory methods permit estimation of the amount of protein thus added?** **R. J. Kent, M.D., Savannah, N. Y.**

ANSWER.—All methods for the determination of serum proteins will give false values if serum is contaminated with hemoglobin. Such contamination should be carefully avoided. It is not possible to make any precise correction, because the presence of hemoglobin in the serum is an indication that there has been incalculable damage to cells which may lead also to transfers of water and inorganic materials and consequent change in the relative volume of the serum. If this is disregarded and it is still desired to determine the amount of serum protein without hemoglobin, it would be necessary to estimate the hemoglobin separately by one of the colorimetric benzidine technics. However, the error in such measurements might be great.

ESTIMATING THE PROTHROMBIN LEVEL

To the Editor:—**Please furnish information on the preparation of Stypven® (venom of Russell's viper) to use for prothrombin estimations. I have tried crystallized crotalic and bothropic venom diluted to 1:100,000, but both clotted plasma before the addition of calcium chloride. Will you discuss the properties of snake venoms and their use for prothrombin estimations.** **M.D., Brazil.**

ANSWER.—According to Eagle (*J. Exper. Med.* **65**:613, 1937) the venoms of Bothrops atrox and Crotalus terrificus basiliscus are able to convert prothrombin to thrombin, or in other words act as thromboplastin. An impurity with thrombic activity in these venoms would account for the clotting of plasma before calcium chloride is added. Neither of these venoms have been used for the determination of prothrombin. Venom from Russell's viper was introduced as a thromboplastin for Quick's prothrombin test by Fullerton (*Lancet* **2**:195, 1940). Recently a number of workers have found that the prothrombin as measured by the one stage method using venom from Russell's viper for thromboplastin may show a relatively high prothrombin level in patients receiving dicumarol® even in the presence of hemorrage and when the level as determined by Quick's original method using acetone-dehydrated rabbit brain is below the margin of safety. The venom from Russell's viper appears therefore to be unreliable for estimating the prothrombin level in patients receiving dicumarol.®

TREATMENT OF SARCOIDOSIS

To the Editor:—A person with Boeck's sarcoid has asked if there is any new treatment of this condition. What is the present treatment?

M.D., Arizona.

ANSWER.—The cause of Boeck-Baumann-Besnier sarcoidosis is still unknown, and no definitive or generally effective mode of therapy has been recorded. Since almost any organ system may become involved with sarcoidosis, treatment, when such is elected, is directed against symptoms. Some of the agents which have been employed include arsenic, bismuth and gold compounds, tuberculin, chaulmoogra oil, roentgen rays, radium and ultraviolet rays. Recently favorable reports have been rendered concerning the use of calciferol and di-hydrotachysterol in cases in which the skin lesions have been the main manifestation. However, toxic side effects may occur which are related apparently to elevation of the serum calcium and nonprotein nitrogen levels; these symptoms may be nausea, vomiting, weakness, malaise and dizziness.

In a recent report from the Conference on Sarcoidosis, held under the auspices of the National Research Council, it is stated that in the natural evolution of the disease "the outcome may be clinical recovery without gross or radiologically visible residuals, or it may be impairment of function of organs involved, or a continuous chronic course of the disease. . . ." In several recorded series of cases in which treatment was not given, about one third of the patients had clinical disappearance of the disease; in one third the disease remained stationary or had alternate progression or regression and in one third it progressed to lethal outcome. Nitrogen mustard has been used in the treatment of 4 patients with sarcoidosis, with some suggestion of therapeutic value. It would seem questionable, however, to employ such a potentially toxic drug in diseases other than malignant lymphatic tumors.

FRAGILITAS OSSIUM

To the Editor:—What is the latest treatment for fragilitas ossium? A small child, whose weight at birth was 3 pounds 3 ounces (1,446 Gm.), progressed rather well until two months ago, when there occurred a fracture of the left femur, then a fracture of the metatarsal bone in the same leg and then a fracture of the tibia and fibula of the same leg. Both the mother and child had negative Kahn reactions. The urine was normal. The child was given vitamin D_2 (drisdol®) with supplementary dicalcium phosphate.

Louis H. Bos, M.D., Reheboth, N. Mex.

ANSWER.—Fragilitas ossium (osteogenesis imperfecta, brittle bones, osteopsathyrosis and sometimes called Löbstein's disease) is characterized by blue scleras, brittle bones and disturbances in hearing (otosclerosis). Many victims of this disease of doubtful hereditary nature suffer skull or rib fractures during the act of birth with fatal intracranial or thoracic hemorrhages. Some infants may reach several years of age before frequent fractures occur. The disease in this last group has been labeled osteogenesis imperfecta tarda. The skull is almost always square shaped and broadened in the parietal axis. The blue scleras according to some authors are never absent; others have reported instances in which blue scleras were not present.

Life expectancy in osteogenesis imperfecta is below normal. Most patients examined fail to show any definite lowering of blood calcium or phosphorus levels, and a few infants show clinically thickened and short stubby bones, whereas most patients with osteogenesis imperfecta tarda show attenuated brittle, easily bent bones with fractures. The dyscrasia is looked on as a congenital lack of proper bone formation. The cortex of long bones is thin, the medullary cavity wide and the bone density in the roentgenogram light. Syphilis is not a cause.

Treatment therefore becomes impotent against prenatal bone malformation. The following methods have been tried. If there is any lowering of calcium and phosphorus blood levels and an absence or low level of free hydrochloric acid in the gastric juice, dilute hydrochloric acid in appropriate doses could be given after meals. A high protein diet is indicated to aid phosphorus intake. Cod liver oil in moderate doses is likewise recommended. Crystalline vitamin D is not recommended. One may use tribasic calcium phosphate in appropriate dosage, watching for any evidence of kidney stone formation. Parathyroid extract should not be administered.

Orthopedic treatment is useful. The fractures usually heal satisfactorily under proper conditions of immobilization. Refracture is frequent. Bone bowing and softening with deformities and laxity of joints are found. The child must be guarded against rough play and trauma and might have to wear supporting braces on the back, legs and/or arms to avoid multiple fractures or skeletal deformities. If the patient survives to full maturity, many of the symptoms may subside, the occurrence of fracture becomes less frequent and life may become more nearly normal. Even the blue scleras may become less intense. These facts have led men to believe that endocrine development had much to do with recovery.

In case of deformities resulting from the fractures, manual osteotomy or multiple, corrective, surgical osteotomy may be employed. All such elected insults to the bone must have prolonged splinting to insure union and to avoid pseudarthrosis. If pseudarthrosis has developed, bone graft may be applied. It is often impossible to obtain bone graft from the patient himself, and in many instances bone from the mother has been satisfactory.

TEMPORARY STERILITY

To the Editor:—A lieutenant in the Air Force who has been stationed on Guam for two years was told after laboratory investigation that he is sterile. He states that a number serving in that area got similar reports. Dr. His, son of the Swiss physiologist, wrote a book entitled "A Doctor at the Front." He mentions the finding of azoospermia in infantry men after tours of front line duty. The lieutenant mentioned he is anxious to know whether the sterility reported is temporary or permanent.

W. A. W. Switzer, M.D., Ridgway, Pa.

ANSWER.—The lieutenant in the Air Force stationed in Guam may be suffering from temporary sterility. A testicular biopsy will determine whether a state of temporary or permanent sterility exists. Great physical or mental exhaustion have been known to result in temporary azoospermia. The condition is frequently found in athletes and teachers.

CALCIUM MEDICATION DURING PREGNANCY

To the Editor:—Is there any evidence that early calcium therapy in the pregnant woman causes the infant's skull to resist molding or cause a more difficult labor? I have used calcium medication for years but feel that deliveries in women are becoming more tedious; with more violence to the mother.

George W. Patterson, M.D., Willits, Calif.

ANSWER.—Good evidence is not available to support the belief that calcium given to pregnant women causes failure of molding or makes labor more difficult. In fact, fully satisfying the maternal need for calcium probably produces beneficial effects with respect to labor pains. Excess calcium given will be excreted unless some abnormal factors are present. This consultant has used it for fifteen years with no evidence of untoward reactions.

LAMINECTOMY AND SCIATICA

To the Editor:—The answers by your consultant to the questions relative to sciatica (The Journal, Jan. 7, 1950, page 70) should not be allowed to stand without comment as representing views unanimously held by all who deal with disk herniations. The answer properly emphasized that sciatica is merely a symptom and implied that operation was indicated for certain disease entities found to be the cause of sciatica. Exception should be taken, however, to the statement, "Laminectomy is indicated when a definitely protruding disk . . . can be demonstrated." The indications for intraspinal surgical intervention in protrusions of lumbar disks involve more than the mere demonstration of a pathologic lesion, since this lesion, unlike tumors and certain infectious conditions, usually does not terminate in an incapacitating or inoperable state if operation is delayed. This being so, one should consider the degree of disability present during the attack, the duration of attacks, the length of the interval between attacks, the total duration of the illness, the age of the patient, the response or lack of it to less radical forms of treatment and the attitude of the patient toward his pain, before advising surgical treatment.

Once operation is decided on it will be necessary only occasionally to perform laminectomy. The answer should have focused attention more on the crucial removal of fragments of cartilage than on one means of gaining access to the intraspinal structures. Laminectomy is unnecessarily radical, and, following the lead of Love, most surgeons remove lower lumbar disk herniations by the interlaminal approach, sometimes aided by the removal of bone from the adjacent margins of the laminas bounding the space in question.

The initial statement by the answering authority, "A positive diagnosis is usually possible by means of spinal fluid analysis for total proteins," also needs comment. Though the total protein is elevated beyond the normal figure in one half to two thirds of patients with disk protrusions, this hardly constitutes a basis for positive diagnosis since a third or half have normal levels and in those with elevated levels it is not the protein elevation which is diagnostic or distinguishes from several other causes of protein excess and sciatica. In practice, the protein level is accepted as auxiliary evidence of herniation if it is between 40 and 120 mg. per hundred cubic centimeters, but if it is much over the higher of these two figures another explanation of the sciatica (neoplasm) becomes likely. The neurologic findings in patients with protruded lumbar disks vary with the disk protruding and the sacral or lumbar roots involved. Attention should not be directed to ankle jerk abnormalities alone among the various reflex and muscular abnormalities possible.

The question concerning the percentage of "cures" to be expected following the removal of protruded disks is ignored in the answer. A number of reports have been made concerning the percentages of various types of results obtained. The "cure" rate (complete relief) ranges from 41.5 per cent to 80 per cent. Additional percentages of patients undergoing operation obtained degrees of relief varying from moderate to almost complete, and these, when added to the cures, raised the percentage of good results.

George Ehni, M.D., Houston, Texas.